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January 14, 2004

JAN 15 2004

C.W. Jameson, Ph.D.
Head, Report on Carinogens
National Toxicology Program
79 Alexander Drive
Building 4401, Room 3118
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Jameson:

Thank you for your November 21, 2003 letter. Although I will not be able to attend the January 27-28 meeting on the Report on Carcinogens and am submitting the following written material.

First, I would like to comment briefly on your review process and evaluation criteria used for listing carcinogens. Regarding your review process, I strongly urge the National Toxicology Program to make a better effort to seek out opinions and data from all possible sources and to fairly evaluate all these sources. The evaluation of specific results relevant to RoC should focus on the quality of the underlying data, the accuracy of the analyses, and the integrity of the investigators. The evaluation should not give credence to inaccurate, unsubstantiated criticisms of the results and ad hominem attacks on the investigators. I am making this recommendation based on the reaction to my May 17, 2003 BMJ paper on environmental tobacco smoke (ETS), coauthored by Dr. Geoffrey C. Kabat. This paper is highly relevant to your classification of environmental tobacco smoke as a "known human carcinogen".

I have enclosed several key items associated with this paper: the full BMJ paper; the BMJ editorial by Dr. George Davey Smith; the rapid response by BMJ editor Richard Smith; the Daily Telegraph (London) press account by Robert Matthews; an August 5, 2003 CMAJ editorial; the August 30, 2003 BMJ letters, authors' reply, and editor's comment; and authors' January 9, 2003 and March 5, 2003 responses to reviewer comments. The entire file related to this paper can be accessed at bmj.com/cgi/content/full/326/7398/1057. All of this material should be carefully read by the appropriate NTP representatives. In addition to its important new findings, this paper provides a good example of the difficulties associated with conducting research on ETS.

Second, because of these new findings, I nominate ETS for delisting as a "known human carcinogen" and for possible reclassification as a "reasonably anticipated human carcinogen". These new findings substantially weaken the already weak US evidence relating ETS and lung cancer and US evidence is most appropriate for making US regulatory decisions. Using spousal smoking history as the measure of ETS exposure, I estimate that a meta-analysis of all US evidence yields an RR(ever exposure/never exposure) ~ 1.10, which is barely significant.

In addition, I am aware of other US evidence in non-journal publications, not included in the above meta-analysis, that do not support a causal relationship between ETS and lung cancer. Finally, I think that substantial publication bias may exist on this subject based on: 1) the difficulties I have experienced with my own publication, 2) the lack of other recent US epidemiologic research on ETS and lung cancer, and 3) the fact that several large relevant US cohorts are not being fully analyzed. I can provide detailed evidence regarding the statements above if the NTP nomination review committee is willing to proceed further with my nomination.

Thank you very much for your consideration.

Sincerely yours,

James E Enstrom

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Enclosures

Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98

James E Enstrom, Geoffrey C Kabat

Abstract

Objective To measure the relation between environmental tobacco smoke, as estimated by smoking in spouses, and long term mortality from tobacco related disease.

Design Prospective cohort study covering 39 years.

Setting Adult population of California, United States.

Participants 118 094 adults enrolled in late 1959 in the American Cancer Society cancer prevention study (CPS I), who were followed until 1998. Particular focus is on the 35 561 never smokers who had a spouse in the study with known smoking habits.

Main outcome measures Relative risks and 95% confidence intervals for deaths from coronary heart disease, lung cancer, and chronic obstructive pulmonary disease related to smoking in spouses and active cigarette smoking.

Results For participants followed from 1960 until 1998 the age adjusted relative risk (95% confidence interval) for never smokers married to ever smokers compared with never smokers married to never smokers was 0.94 (0.85 to 1.05) for coronary heart disease, 0.75 (0.42 to 1.35) for lung cancer, and 1.27 (0.78 to 2.08) for chronic obstructive pulmonary disease among 9619 men, and 1.01 (0.94 to 1.08), 0.99 (0.72 to 1.37), and 1.13 (0.80 to 1.58), respectively, among 25 942 women. No significant associations were found for current or former exposure to environmental tobacco smoke before or after adjusting for seven confounders and before or after excluding participants with pre-existing disease. No significant associations were found during the shorter follow up periods of 1960-5, 1966-72, 1973-85, and 1973-98.

Conclusions The results do not support a causal relation between environmental tobacco smoke and tobacco related mortality, although they do not rule out a small effect. The association between exposure to environmental tobacco smoke and coronary heart disease and lung cancer may be considerably weaker than generally believed.

Introduction

Several major reviews have determined that exposure to environmental tobacco smoke increases the relative risk of coronary heart disease, based primarily on comparing never smokers married to smokers with never smokers married to never smokers. The American Heart Association, the California Environmental Protection Agency, and the US surgeon general have concluded that the increase in coronary heart disease risk due to environmental tobacco smoke is 30% (relative risk 1.30).[1-3] Meta-analyses of epidemiological studies have reported summary relative risks (95% confidence intervals) of 1.30 (1.22 to 1.38), 1.25 (1.17 to 1.32), and 1.25 (1.17 to 1.33) for coronary heart disease[4-6] and 1.23 (1.13 to 1.35) and 1.23 (1.13 to 1.34) for lung cancer,[7 8] similar to the 1.20 found by the California Environmental Protection Agency and the US surgeon general.[2 3] The US Environmental Protection Agency has classified environmental tobacco smoke as a known human carcinogen.[7] Chronic obstructive pulmonary disease, primarily asthma, bronchitis, and emphysema, has been associated with exposure to environmental tobacco smoke, but the evidence for increased mortality is sparse.[2 3]

Although these reviews come to similar conclusions, the association between environmental tobacco smoke and tobacco related diseases is still controversial owing to several limitations in the epidemiological studies.[9-14] Exposure to environmental tobacco smoke is difficult to measure quantitatively and therefore has been approximated by self reported estimates, primarily smoking history in spouses. Confounding by active cigarette smoking is so strong that the association with environmental tobacco smoke can only be evaluated among never smokers. The relation between tobacco related diseases and environmental tobacco smoke may be influenced by misclassification of some smokers as never smokers, misclassification of exposure status to environmental tobacco smoke, and several potential confounders. It is also unclear how the reported increased risk of coronary heart disease due to environmental tobacco smoke could be so close to the increased risk due to active smoking (30% and 70%, respectively), since environmental tobacco smoke is much more dilute than actively inhaled smoke.

Most epidemiological studies have found that environmental tobacco smoke has a positive but not statistically significant relation to coronary heart disease and lung cancer. Meta-analyses have combined these inconclusive results to produce statistically significant summary relative risks.[4-8] However, there are problems inherent in using meta-analysis to establish a causal relation.[9-14] The epidemiological data are subject to the limitations described above. They have not been collected in a standardised way, and some relative risks

Editorial by Davey Smith

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Table 1 Follow up details of 51 343 men and 66 751 women in California cancer prevention study (CPS I) cohort

	Total cohort		Never smokers*	
Follow up category	**Men**	**Women**	**Men**	**Women**
1 Jan 1960:				
Dead, deleted from file (1 Oct to 31 Dec 1959)	22	14		
Alive, completed 1959 questionnaire (1 Oct 1959 to 31 Mar 1960)	51 321	66 737	9619	25 942
31 Dec 1965:				
Dead, ICD codes (1 Jan 1960 to 31 Dec 1965)	4 907	3 506	685	868
Dead, no ICD codes(1 Jan 1960 to 31 Dec 1965)	45	47	7	13
Withdrawn (1 Jan 1960 to 30 Sep 1965)†	718	974	79	257
Lost (1 Jan 1960 to 31 Dec 1965)‡	31	49	4	13
Alive, completed Sep 1965 questionnaire	44 757	61 079	8574	24 077
Alive, follow up to 31 Dec 1998	863	1 082	270	714
31 Dec 1972:				
Dead, ICD codes(1 Jan 1960 to 31 Dec 1972)	12 295	9 446	1865	2 634
Dead, no ICD codes (1 Jan 1960 to 31 Dec 1972)	146	160	19	41
Withdrawn (1 Jan 1960 to 30 Sep 1971)†	1 222	2 825	164	984
Lost (1 Jan 1960 to 31 Dec 1972)	1 525	3 367	269	1 103
Alive, completed Sep 1972 questionnaire	26 070	37 926	5455	16 171
Alive, follow up to 31 Jan 1998	10 063	13 013	1847	5 009
31 Dec 1998:				
Dead, ICD codes (1 Jan 1960 to 31 Dec 1998)	37 554	36 669	6673	13 160
Dead, no ICD codes (1 Jan 1960 to 31 Dec 1998)	2 456	2 722	464	1 130
Withdrawn (1 Jan 1960 to 30 Sep 1972)†	1 395	5 450	197	2 105
Lost (1 Jan 1960 to 31 Dec 1998)	2 962	6 953	560	2 579
Alive, correctly completed 1999 questionnaire	2 290	4 869	681	2 413
Alive, matched with California driver's licence and not known dead§	4 664	10 074	1044	4 555

*Never smokers who had spouse in cohort with known smoking habits.
†Further follow up not possible because of incomplete or missing name on 1972 master database.
‡Complete name on 1972 master file and no match with California driver's licence file, California death file, or social security death index until 1998.
§Based on 1990-9 match with California driver's licence file and no death match with California death file or social security death index during 1960-98.

have been inappropriately combined. Because it is more likely that positive associations get published, unpublished negative results could reduce the summary relative risks. Also, the meta-analyses of coronary heart disease omitted the published negative results from the large American Cancer Society cancer prevention study (CPS I).[10 11] We have extended the follow up for the California participants in this cohort, analysed the relation between environmental tobacco smoke and tobacco related diseases, and addressed concerns about this study.

Methods

CPS I is a prospective cohort study begun by the American Cancer Society in October 1959 and

Table 2 Personal and lifestyle characteristics of male 1959 never smokers in California cancer prevention study (CPS I) cohort by smoking status of spouse

	Smoking status of spouse, 1959						1999 respondents	
			Current (cigarettes/day)					
Characteristic	**Never**	**Former**	**1-19**	**20-39**	**≥40**	**Total**	**1959 value**	**1999 value**
No of participants in 1959	7458	624	905	587	45	9619		
No of participants in 1999	498	59	69	51	4	681	681	681
Withdrawn as of 1972 (%)	2.0 (146)	2.4 (15)	2.1 (19)	2.7 (16)	2.2 (1)	2.0 (197)		
Lost to follow up as of 1999 (%)	5.9 (441)	4.6 (29)	5.4 (49)	6.3 (37)	8.9 (4)	5.8 (560)		
Unknown cause of death (%)	6.6 (371)	6.1 (26)	6.6 (42)	5.4 (22)	8.8 (3)	6.5 (464)		
Widowed as of 1999	28.2 (1649)	25.1 (124)	31.9 (231)	38.1 (174)	39.4 (13)	29.0 (2191)		
Mean age (years) at enrolment	56.5 (7458)	51.9 (624)	52.8 (905)	51.7 (587)	52.6 (45)	55.5 (9619)	45.5 (681)	45.5 (681)
White people (%)	97.8 (7292)	98.6 (615)	98.0 (887)	98.1 (577)	100.0 (45)	97.9 (9416)	98.6 (672)	
Education ≥12 years (%)	67.3 (5017)	80.6 (403)	71.3 (645)	74.2 (436)	84.5 (38)	69.0 (6639)	89.0 (606)	92.9 (633)
Mean height (cm)	175.8 (7328)	176.3 (614)	176.3 (898)	176.5 (582)	176.8 (43)	175.8 (9465)	177.0 (681)	175.3 (681)
Mean weight (kg)	78.9 (7137)	79.7 (602)	79.6 (881)	80.9 (573)	82.2 (44)	79.1 (9237)	78.6 (681)	74.9 (681)
History of serious diseases (%):	13.8 (965)	10.0 (59)	11.9 (102)	11.9 (65)	12.5 (5)	13.3 (1196)	4.1 (28)	
Cancer	5.0 (369)	4.7 (29)	5.5 (50)	4.6 (27)	2.2 (1)	5.0 (476)	2.9 (20)	39.9 (272)
Heart disease	7.0 (471)	4.8 (27)	5.4 (44)	5.6 (29)	7.7 (3)	6.6 (574)	1.0 (7)	
Stroke	1.8 (125)	0.5 (3)	1.0 (8)	1.7 (9)	2.6 (1)	1.7 (146)	0.2 (1)	
Sick at present time (%)	6.4 (475)	4.8 (30)	6.3 (57)	5.6 (33)	4.4 (2)	6.2 (597)	4.2 (29)	22.2 (151)
Professional occupation (%)	14.3 (1068)	14.9 (93)	11.1 (100)	10.5 (62)	17.8 (8)	13.8 (1331)	17.8 (121)	
Urban residence (%)	85.9 (6404)	90.7 (566)	88.7 (803)	90.0 (529)	88.9 (40)	86.7 (8342)	86.0 (586)	
Moderate or heavy exercise (%)	76.2 (5683)	70.2 (438)	72.5 (656)	71.1 (418)	57.8 (26)	75.0 (7221)	70.7 (481)	70.9 (483)
Eat green salads (mean days/week)	4.8 (7201)	4.9 (617)	5.0 (887)	5.0 (573)	4.9 (45)	4.8 (9323)	5.1 (681)	4.5 (681)
Eat fruits or drink fruit juice (mean days/week)	6.0 (7226)	6.0 (614)	5.9 (886)	5.5 (574)	5.3 (43)	5.9 (9343)	5.9 (681)	5.6 (681)
Often use vitamin pills (%)	38.1 (2841)	39.7 (248)	33.2 (300)	28.7 (169)	42.2 (19)	37.2 (3577)	34.0 (232)	79.2 (539)

Some values do not agree with denominators due primarily to missing data.

described in detail elsewhere.[15-17] A total of 1 078 894 adults from 25 states were enrolled on the basis of a detailed four page questionnaire. In 1961, 1963, 1965, and 1972, surviving cohort members completed brief questionnaires. The American Cancer Society ascertained the vital status and current address for most of

Table 3 Personal and lifestyle characteristics of female 1959 never smokers in California cancer prevention study (CPS I) cohort by smoking status of spouse

	Smoking status of spouse, 1959							1999 respondents	
			Current status*						
Characteristic	Never	Former	Pipe or cigar	1-19	20-39	≥40	Total	1959 value	1999 value
No of participants in 1959	7399	6858	2691	3219	4934	841	25 942		
No of participants in 1999	788	573	252	233	479	87	2 412	2412	2412
Withdrawn as of 1972 (%)	8.1 (602)	8.1 (558)	8.1 (219)	8.2 (265)	7.7 (380)	9.6 (81)	8.1 (2 105)		
Lost to follow up as of 1999 (%)	9.8 (722)	9.8 (669)	9.7 (260)	10.1 (324)	10.4 (513)	10.8 (91)	9.9 (2 579)		
Unknown cause of death (%)	7.6 (304)	7.7 (305)	7.2 (111)	8.1 (149)	8.7 (218)	10.4 (43)	7.9 (1 130)		
Widowed as of 1999 (%)	59.7 (3464)	65.2 (3528)	64.2 (1368)	69.6 (1774)	73.4 (2859)	75.1 (480)	66.0 (13 473)		
Mean age (years) at enrolment	53.1 (7399)	54.5 (6858)	54.4 (2691)	53.7 (3219)	50.9 (4934)	49.8 (841)	53.1 (25 942)	44.5 (2412)	44.5 (2412)
White people (%)	97.6 (7225)	98.5 (6759)	97.8 (2631)	95.9 (3088)	97.9 (4828)	98.7 (831)	97.8 (25 362)	98.0 (2364)	
Education ≥12 years (%)	73.7 (5452)	68.2 (4685)	68.9 (1853)	65.6 (2109)	70.4 (3476)	77.2 (650)	70.2 (18 225)	87.9 (2120)	93.0 (2243)
Mean height (cm)	162.1 (7232)	161.8 (6706)	161.8 (2640)	161.5 (3168)	161.8 (4846)	162.3 (822)	161.8 (25 414)	162.6 (2412)	161.3 (2412)
Mean weight (kg)	63.9 (7085)	63.8 (6596)	64.0 (2581)	63.5 (3097)	63.7 (4777)	63.64 (824)	63.8 (24 960)	61.4 (2412)	62.3 (2412)
History of serious diseases (%):	11.8 (834)	12.8 (857)	11.3 (293)	10.2 (315)	10.1 (483)	10.2 (85)	11.4 (2 867)	5.8 (140)	
Cancer	5.8 (427)	6.7 (465)	5.8 (156)	5.2 (167)	5.9 (293)	7.2 (61)	6.0 (1 569)	4.1 (99)	36.4 (878)
Heart disease	5.1 (347)	5.1 (330)	4.7 (117)	4.2 (123)	3.4 (154)	2.9 (23)	4.5 (1 094)	1.5 (36)	
Stroke	0.9 (60)	1.0 (62)	0.8 (20)	0.8 (25)	0.8 (36)	0.1 (1)	0.9 (204)	0.2 (5)	
Sick at present time (%)	7.9 (586)	8.3 (572)	8.6 (231)	8.2 (264)	8.8 (436)	8.8 (74)	8.3 (2 163)	6.4 (154)	19.7 (475)
Professional occupation (%)	14.6 (1080)	12.8 (881)	13.0 (350)	12.9 (414)	10.6 (523)	10.9 (92)	12.9 (3 340)	17.4 (420)	
Urban residence (%)	85.8 (6349)	86.4 (5929)	85.4 (2298)	86.2 (2775)	85.7 (4229)	85.8 (722)	85.9 (22 302)	84.7 (2043)	
Moderate or heavy exercise (%)	82.5 (6097)	82.5 (5649)	83.3 (2242)	82.8 (2665)	82.3 (4058)	81.0 (681)	82.6 (21 392)	80.2 (1934)	65.5 (1580)
Eat green salads (mean days/week)	5.1 (7219)	5.0 (6701)	5.1 (2618)	4.9 (3122)	5.1 (4835)	5.1 (825)	5.0 (25 320)	5.4 (2412)	4.6 (2412)
Eat fruits or drink fruit juice (mean days/week)	6.4 (7227)	6.3 (6727)	6.3 (2621)	6.1 (3132)	6.0 (4846)	6.0 (826)	6.2 (25 379)	6.1 (2412)	5.6 (2412)
Often use vitamin pills (%)	40.4 (2985)	39.8 (2728)	38.2 (1028)	36.8 (1183)	35.3 (1739)	34.0 (286)	38.4 (9 949)	38.3 (924)	81.2 (1958)

*Cigar, pipe, or number of cigarettes consumed per day.
Some values do not agree with denominators due primarily to missing data.

Table 4 Percentage of cohort exposed to three measures of environmental tobacco smoke in 1999 by smoking status of spouse among 1959 never smokers who responded to 1999 follow up questionnaire. Subgroup of 1959 never smokers aged ≥50 years at entry (born before 1910) also shown. Values are percentage (number) exposed to environmental tobacco smoke in 1999, except for data on marital status

			Regular exposure to cigarette smoke from others in work or daily life			Married only once as of 1999	
Smoking status of spouse in 1959	Lived with smoker	Lived with smoking spouse	None	Light	Moderate or heavy	Current	Ever
1959 male never smokers							
Never (n=496)	24.0 (115)	3.8 (18)	43.5 (189)	34.5 (150)	22.1 (96)	66.2 (319)	82.2 (398)
Former (n=59)	53.5 (31)	27.6 (16)	20.8 (11)	43.4 (23)	35.9 (19)	62.5 (35)	78.6 (44)
Current (n=124)	89.5 (111)	75.0 (93)	23.1 (27)	38.5 (45)	38.5 (45)	45.1 (55)	70.5 (86)
1959 female never smokers							
Never (n=788)	32.5 (253)	3.7 (29)	61.7 (398)	24.3 (157)	14.0 (90)	39.5 (306)	89.2 (686)
Former (n=573)	73.6 (421)	55.2 (316)	41.3 (196)	26.5 (126)	32.2 (153)	32.6 (187)	84.0 (474)
Current:							
Pipe or cigar (n=252)	84.7 (211)	69.9 (174)	34.0 (73)	30.2 (65)	35.8 (77)	30.1 (75)	82.2 (198)
1-19 cigarettes/day (n=233)	93.0 (212)	83.3 (190)	25.5 (53)	28.8 (60)	45.7 (95)	22.0 (50)	80.4 (180)
20-39 cigarettes/day (n=479)	98.7 (467)	91.1 (431)	19.7 (84)	20.9 (89)	59.4 (253)	16.4 (78)	78.5 (365)
≥40 cigarettes/day (n=87)	98.8 (84)	83.5 (71)	16.2 (13)	12.5 (10)	71.3 (57)	14.8 (13)	73.9 (65)
Total of current smokers (1051)	94.1 (974)	83.7 (866)	24.0 (223)	24.1 (224)	51.9 (482)	20.8 (216)	79.4 (808)
1959 male never smokers aged ≥50 years at enrolment							
Never (n=94)	11.5 (10)	2.3 (2)	58.2 (46)	24.1 (19)	17.7 (12)	47.8 (43)	80.0 (72)
Former (n=11)	36.4 (4)	18.2 (2)	50.0 (5)	20.0 (2)	30.0 (3)	45.5 (5)	90.9 (10)
Current (n=17)	88.2 (15)	70.6 (12)	18.8 (3)	43.7 (7)	37.5 (6)	12.5 (2)	56.3 (9)
1959 female never smokers aged ≥50 years at enrolment							
Never (n=100)	26.0 (26)	4.0 (4)	71.2 (52)	21.9 (16)	6.9 (5)	16.3 (16)	92.7 (89)
Former (n=99)	83.0 (78)	68.1 (64)	40.7 (33)	24.7 (20)	34.6 (28)	17.2 (17)	80.4 (78)
Current:							
Pipe or cigar (n=43)	71.4 (30)	59.5 (25)	42.5 (14)	24.2 (8)	33.3 (11)	14.0 (6)	77.8 (28)
1-19 cigarettes/day (n=29)	96.3 (26)	85.2 (23)	20.0 (5)	28.0 (7)	52.0 (13)	6.9 (2)	84.6 (22)
20-39 cigarettes/day (n=75)	97.1 (72)	87.7 (67)	14.8 (7)	21.9 (13)	63.3 (43)	7.9 (6)	81.7 (58)
≥40 cigarettes/day (n=9)	100.0 (8)	75.0 (6)	0	0	100.0 (7)	11.1 (1)	88.9 (8)
Total of current smokers (n=156)	90.7 (136)	80.7 (121)	20.3 (26)	21.9 (28)	57.8 (74)	9.6 (15)	81.7 (116)

Some values do not agree with denominators due primarily to missing data.

Table 5 One measure of exposure to environmental tobacco smoke as of 1999 by smoking history of spouse in 1999 among 1959/1999 never smokers who responded to 1999 follow up questionnaire. Values are percentage (number) exposed to environmental tobacco smoke in 1999

	Regular exposure to cigarette smoke from others in work or daily life			
Ever lived with a smoking spouse	**None**	**Light**	**Moderate**	**Heavy**
1959/1999 male never smokers				
No (n=336)	50.0 (168)	33.9 (114)	14.9 (50)	1.2 (4)
Yes:				
No smoking nearby (n=23)	30.4 (7)	52.2 (12)	17.4 (4)	0
Exposed 1-19 years (n=17)	17.6 (3)	29.4 (5)	41.2 (7)	11.8 (2)
Exposed 20-39 years (n=35)	20.0 (7)	48.6 (17)	20.0 (7)	11.4 (4)
Exposed 40-80 years (n=33)	6.1 (2)	27.3 (9)	57.5 (19)	9.1 (3)
1959/1999 female never smokers				
No (n=570)	76.7 (437)	16.1 (92)	5.3 (30)	1.9 (11)
Yes:				
No smoking nearby (n=122)	36.9 (45)	36.9 (45)	23.7 (29)	2.5 (3)
Exposed 1-19 years (n=162)	29.0 (47)	38.9 (63)	27.2 (44)	4.9 (8)
Exposed 20-39 years (n=355)	19.7 (70)	24.5 (87)	44.5 (158)	11.3 (40)
Exposed 40-80 years (n=323)	14.1 (46)	20.5 (66)	44.3 (143)	21.1 (68)
1959/1999 male never smokers aged ≥50 years at enrolment				
No (n=70)	62.9 (44)	24.3 (17)	11.4 (8)	1.4 (1)
Yes:				
No smoking nearby (n=3)	33.3 (1)	33.3 (1)	33.3 (1)	0
Exposed 1-19 years (n=2)	0	50.0 (1)	0	50.0 (1)
Exposed 20-39 years (n=5)	20.0 (1)	60.0 (3)	20.0 (1)	0
Exposed 40-80 years (n=5)	20.0 (1)	0	60.0 (3)	20.0 (1)
1959/1999 female never smokers aged ≥50 years at enrolment				
No (n=73)	89.0 (65)	9.6 (7)	0	1.4 (1)
Yes:				
No smoking nearby (n=20)	25.0 (5)	60.0 (12)	10.0 (2)	5.0 (1)
Exposed 1-19 years (n=20)	55.0 (11)	40.0 (8)	5.0 (1)	0
Exposed 20-39 years (n=48)	8.3 (4)	16.7 (8)	62.5 (30)	12.5 (6)
Exposed 40-80 years (n=66)	15.2 (10)	18.2 (12)	45.4 (30)	21.2 (14)

Some values do not agree with denominators due primarily to missing data.

the adults up to September 1972 and obtained death certificates for most of those known dead.

Follow up

Long term follow up was undertaken at the University of California at Los Angeles on all 118 094 participants from California. This is described in detail elsewhere and summarised in table 1.[18] The participants were matched several times with the California death file and the social security death index on the basis of their name and other identifying variables.[18 19] Overall, 79 437 deaths were identified up to 31 December 1998, and the underlying cause was obtained from the California death file and death certificates for 93% (73 876) of these deaths.

Participants were also matched with information given on their California driver's licence, based primarily on name, date of birth, and height. We obtained the address given during the 1990s for 21 897 participants who were not known as dead as of 1999, and these participants were assumed to be alive in 1999. Of the remaining participants in the study's master database, 6845 were withdrawn from further follow up as of September 1972 because their complete name was not retained, and 9915 were lost to follow up as of 1999 because their vital status was unknown.

To assess the current status of surviving cohort members, in mid-1999 we sent out a two page questionnaire on smoking and lifestyle to those participants with an address for 1995 or later on their driver's licence. Overall, 2290 of 5275 men (43.4%) and 4869 of 10 738 women (45.3%) completed the questionnaire. Responses to name, date of birth, and height on the questionnaire confirmed that over 99% of the respondents had been accurately located.

The follow up period was from time of entry to the study (1 January to 31 March 1960) until death, withdrawal (date last known alive), or end of follow up (31 December 1998). The participants were aged 30-96 years at enrolment. We excluded the few person years of observation and the 36 deaths during 1959. The underlying cause of each death was assigned according to the international classification of diseases (seventh, eighth, or ninth revisions). Coronary heart disease was defined as 420 (ICD-7) during 1960-7, 410-4 (ICD-8) during 1968-78, and 410-4 (ICD-9) during 1979-98, lung cancer was defined as 162-3 (ICD-7), 162 (ICD-8), and 162 (ICD-9), and chronic obstructive pulmonary disease was defined as 241, 500-2, and 527.1 (ICD-7), 490-3 (ICD-8), and 490-6 (ICD-9). For the analysis of environmental tobacco smoke we selected the 35 561 participants who had never smoked as of 1959 and who had a spouse in the study with known smoking habits.

Statistical analysis

The independent variable used for analysis was exposure to environmental tobacco smoke based on smoking status of the spouse in 1959, 1965, and 1972. Never smokers married to current or former smokers were compared with never smokers married to never smokers. The 1959 never smokers were defined as those who had never smoked any form of tobacco as of 1959. The 1965 never smokers were defined as 1959 never smokers who did not smoke cigarettes as of 1965. The 1972 never smokers were defined as 1959

never smokers who did not smoke cigarettes as of 1965 and 1972. The 1959/1999 never smokers were defined as 1959 never smokers who had never smoked cigarettes as of 1999. Never smokers married to a current smoker were subdivided into categories according to the smoking status of their spouse: 1-9, 10-19, 20, 21-39, ≥40 cigarettes consumed per day for men and women, with the addition of pipe or cigar usage for women. Former smokers were considered as an additional category.

We calculated the age adjusted relative risk of death and 95% confidence interval as a function of smoking status of the spouse by using Cox proportional hazards regression.[18 20] A fully adjusted relative risk was calculated by using a model that included age and seven potential confounders at baseline: race (white, non-white), education level (<12, 12, >12 years), exercise (none or slight, moderate, heavy), body mass index (<20, 20-22.99, 23-25.99, 26-29.99, ≥30), urbanisation (five population sizes), fruit or fruit juice intake (0-2, 3-4, 5-7 days a week), and health status (good, fair, poor, sick). Analyses were carried out for all participants and for healthy participants (those with no history of cancer, heart disease, or stroke at baseline). The relative risk was also calculated for current cigarette smokers (cigarettes only) as a function of number of cigarettes consumed per day for the entire cohort.[18] For reference, the age adjusted death rate has been calculated by cause of death for all never smokers.[18]

Results

The personal and lifestyle characteristics and follow up status for 1959 never smokers were relatively independent of their spouse's smoking status (tables 2 and 3). Also, the baseline characteristics of the 1999 respondents in 1959 were similar to those for all participants in 1959, except for a younger age at enrolment. Although heavily censored by age, the 1999 respondents seemed reasonably representative of survivors. Race, education, exercise, height, weight, and fruit intake had also remained largely unchanged among the 1999 respondents since 1959. The proportion of participants who had withdrawn as of 1972, were lost as of 1999, or had an unknown cause of death was not related to the smoking status of spouses. However, widowhood (widowed as of 1999) increased substantially with the level of smoking in the spouse.

The smoking status of spouses as of 1959 was related to three self reported measures of exposure to environmental tobacco smoke as of 1999 (table 4). Particularly for women, there was a clear relation between smoking status of spouses as of 1959 and self reported measures in 1999 of having lived with a smoker, having lived with a smoking spouse, and a positive answer to the question "In your work or daily life, are (were) you regularly exposed to cigarette smoke from others?" Also, the percentage of participants currently married as of 1999 declined substantially with the smoking status of the spouse, owing to increased widowhood.

Table 6 Percentage of current smokers by cigarettes consumed per day as of 1965, 1972, and 1999, and former smokers by year of cessation as of 1999 among 1959 never smokers by smoking status of spouse. Values are percentages (numbers) of cigarette smokers

	Current smoking as of 1965 (cigarettes/day)		Current smoking as of 1972 (cigarettes/day)		Cigarette smoking as of 1999		
1959 spousal smoking	1-9	≥10	1-9	≥10	Current	Former (quit <1990)	Former (quit ≥1990)
1959 male never smokers							
	(n=8 602)		(n=5 479)			(n=679)	
Never	0.3 (16)	0.8 (36)	0.2 (5)	0.2 (8)	0.2 (1)	5.2 (24)	0.7 (3)
Former	0.4 (2)	1.2 (6)	0	0.8 (2)	0	15.3 (8)	0
Current	0.7 (8)	2.0 (25)	0.3 (3)	0.5 (4)	0	6.5 (8)	1.6 (2)
1959 female never smokers							
	(n=24 112)		(n=16 237)			(n=2 412)	
Never	0.3 (16)	0.4 (19)	0.3 (9)	0.4 (12)	0.3 (2)	2.8 (16)	1.4 (8)
Former	0.5 (24)	0.4 (25)	0.2 (9)	0.3 (9)	0.2 (1)	5.0 (22)	0.9 (4)
Current:							
Pipe or cigar	0.6 (15)	0.4 (9)	0.6 (7)	0.4 (4)	0.4 (1)	1.8 (3)	1.8 (3)
1-19 cigarettes/day	0.8 (21)	0.9 (22)	0.6 (9)	0.5 (7)	0	1.7 (4)	2.2 (5)
20-39 cigarettes/day	1.0 (41)	1.2 (52)	0.5 (13)	0.6 (15)	0.2 (1)	1.4 (6)	1.7 (7)
≥40 cigarettes/day	1.4 (10)	1.6 (11)	0.6 (3)	0.2 (1)	1.1 (1)	6.4 (5)	3.9 (3)
Total of current smokers	0.9 (87)	0.9 (94)	0.6 (32)	0.5 (27)	0.3 (3)	2.0 (18)	2.0 (18)
1959 male never smokers aged ≥50 years at enrolment							
	(n=5 521)		(n=3 306)			(n=122)	
Never	0.3 (10)	0.8 (23)	0.1 (1)	0.2 (4)	0	5.3 (5)	0
Former	0	1.4 (4)	0	0	0	9.1 (1)	0
Current	0.6 (4)	2.5 (16)	0	0.6 (3)	0	11.8 (2)	0
1959 female never smokers aged ≥50 years at enrolment							
	(n=14 014)		(n=8 957)			(n=355)	
Never	0.2 (6)	0.3 (6)	0.3 (4)	0.3 (4)	0	1.0 (1)	0
Former	0.1 (4)	0.5 (13)	0.2 (4)	0	0	7.1 (7)	0
Current:							
Pipe or cigar	0.2 (3)	0.2 (4)	0.4 (1)	0	0	2.3 (1)	0
1-19 cigarettes/day	0.4 (5)	0.8 (12)	0.3 (2)	0.6 (4)	0	3.4 (1)	0
20-39 cigarettes/day	0.7 (14)	0.9 (20)	0.5 (5)	0.5 (4)	1.3 (1)	0	2.7 (2)
≥40 cigarettes/day	0.6 (2)	1.6 (5)	0.8 (2)	0	0	0	0
Total of current smokers	0.4 (24)	0.8 (41)	0.4 (10)	0.4 (8)	0.6 (1)	1.3 (2)	1.3 (2)

Some values do not agree with denominators due primarily to missing data.

Table 7 Level of smoking in spouse and deaths from selected causes among male never smokers in California cancer prevention study (CPS I) cohort, as of 1959 and 1972. Relative risk (95% confidence interval) comparing individuals with each level of exposure to those without exposure. Proportional hazards linear models adjusted for age and for age and seven confounders. For reference, 1960-98 death rate in deaths per 1000 person years adjusted to 1960 US population for attained ages 35-84 is given[18]

	All 1959 participants, followed 1960-98			1959 participants aged ≥50, followed 1960-98		Participants defined in 1972, followed 1973-98	
Smoking in spouse and cause of death	No of deaths/No of participants	Age adjusted relative risk (95% CI)	Fully adjusted relative risk (95% CI)	No of deaths/No of participants	Age adjusted relative risk (95% CI)	No of deaths/No of participants	Age adjusted relative risk (95% CI)
Coronary heart disease (death rate 3.05/1000)							
Never (1)*	1860/7458	1.00	1.00	1534/5201	1.00	806/3404	1.00
Former (2)*	126/624	0.94 (0.78 to 1.12)	0.94 (0.77 to 1.14)	83/323	0.93 (0.74 to 1.16)	114/573	0.94 (0.77 to 1.14)
Current (cigarettes/day):							
1-9 (3)*	81/392	0.97 (0.78 to 1.21)	0.98 (0.78 to 1.24)	59/230	1.00 (0.77 to 1.30)	20/89	1.32 (0.84 to 2.06)
10-19 (4)*	99/513	0.86 (0.70 to 1.05)	0.82 (0.66 to 1.02)	73/282	0.91 (0.72 to 1.15)	33/153	1.02 (0.72 to 1.45)
20 (5)*	81/458	0.92 (0.74 to 1.15)	0.89 (0.70 to 1.13)	58/245	1.02 (0.78 to 1.32)	35/189	0.94 (0.67 to 1.32)
21-39 (6)*	27/129	1.16 (0.79 to 1.69)	1.13 (0.76 to 1.68)	19/62	1.30 (0.82 to 2.04)	14/58	1.20 (0.70 to 2.03)
≥40 (7)*	13/45	1.29 (0.75 to 2.22)	1.24 (0.70 to 2.19)	9/26	1.25 (0.65 to 2.41)	4/36	0.65 (0.24 to 1.73)
Total of current smokers	301/1537	0.94 (0.83 to 1.07)	0.92 (0.80 to 1.05)	218/845	1.00 (0.87 to 1.15)	106/525	1.04 (0.85 to 1.27)
Ever	427/2161	0.94 (0.85 to 1.05)	0.93 (0.83 to 1.04)	301/1168	0.98 (0.86 to 1.11)	220/1098	0.99 (0.85 to 1.15)
7 level index	2287/9619	0.99 (0.95 to 1.02)	0.98 (0.94 to 1.02)	1835/6369	1.00 (0.96 to 1.05)	1026/4502	1.00 (0.95 to 1.05)
Lung cancer (death rate 0.11/1000)							
Never	65	1.00	1.00	50	1.00	27	1.00
Former	5	0.92 (0.37 to 2.30)	0.82 (0.29 to 2.26)	3	0.89 (0.28 to 2.88)	3	0.63 (0.19 to 2.09)
Current	9	0.69 (0.34 to 1.39)	0.57 (0.26 to 1.26)	5	0.60 (0.24 to 1.52)	1	0.23 (0.03 to 1.68)
Ever	14	0.75 (0.42 to 1.35)	0.63 (0.33 to 1.22)	8	0.69 (0.32 to 1.46)	4	0.43 (0.15 to 1.24)
7 level index	79	0.94 (0.77 to 1.14)	0.88 (0.70 to 1.10)	58	0.91 (0.71 to 1.17)	31	0.68 (0.41 to 1.13)
Chronic obstructive pulmonary disease (death rate 0.12/1000)							
Never	69	1.00	1.00	59	1.00	30	1.00
Former	5	0.95 (0.38 to 2.37)	1.00 (0.40 to 2.50)	4	1.09 (0.40 to 3.02)	4	0.88 (0.31 to 2.50)
Current	17	1.40 (0.82 to 2.40)	1.28 (0.72 to 2.27)	13	1.51 (0.82 to 2.78)	7	1.80 (0.78 to 4.17)
Ever	22	1.27 (0.78 to 2.08)	1.20 (0.72 to 2.00)	17	1.39 (0.81 to 2.41)	11	1.29 (0.64 to 2.61)
7 level index	91	1.06 (0.91 to 1.25)	1.05 (0.88 to 1.24)	76	1.09 (0.91 to 1.30)	41	1.08 (0.86 to 1.38)

*Values in parentheses are index level of environmental tobacco smoke.

Smoking history of the spouse as assessed in 1999 was strongly related to exposure to environmental tobacco smoke as of 1999 for both men and women (table 5).

Misclassification of exposure and smoking status

Although there was substantial misclassification of environmental tobacco smoke exposure status from 1959 to 1999, it was less for those never smokers aged 50 or over at enrolment (see table 4), never smokers defined in 1972 (data not shown), and never smokers defined in 1999 (see table 5). Misclassification of exposure status produces a measured relative risk that is closer to 1.0 than the true relative risk.[8 15] The extent of misclassification from 1959 to 1999 could not obscure a true association with a relative risk of about 1.3, if it exists, among women, but it could largely obscure this association among men. However, this level of misclassification, which is based on the changes that occurred over 40 years among the younger than average 1999 respondents, exaggerates the true level of misclassification that occurred among the cohort as a whole, particularly during short follow up periods.

Essentially all 1959 never smokers remained never smokers on the basis of smoking status reported in 1965, 1972, and 1999 (table 6). Of those who reported a history of smoking in 1999, most had smoked no more than 10 cigarettes per day for a few years, and most had quit smoking before 1960. This indicates only a small degree of misclassification of smoking status. Some bias exists in the misclassification of smoking status among the 1959 never smokers, because the percentage who smoked in the 1965 and 1972 surveys was greatest among those with the highest levels of smoking in spouses. This bias produces a measured relative risk that is greater than the true relative risk, but by a negligible amount for this level of bias.[8 15]

Effect of exposure to environmental tobacco smoke

Exposure to environmental tobacco smoke was not significantly associated with the death rate for coronary heart disease, lung cancer, or chronic obstructive pulmonary disease in men or women (tables 7 and 8). This was true for all 1959 never smokers and 1959 never smokers aged 50 or over at enrolment followed during 1960-98 and for 1972 never smokers followed during 1973-98. The relative risks were slightly reduced after adjustment for seven confounders. Results were essentially unchanged among the healthy participants only (data not shown). The relative risks were consistent with 1.0 for virtually every level of exposure to environmental tobacco smoke, current or former. Only the relative risks for chronic obstructive pulmonary disease suggested an association. An environmental tobacco smoke index based on seven or eight levels of smoking in a spouse yielded a relative risk of about 1.0 for each level of change and no suggestion of a dose-response trend.

In addition, analyses for coronary heart disease were performed for three short follow up periods with presumably smaller misclassification errors. All relative risks for coronary heart disease were consistent with 1.0 for the follow up periods of 1960-5, 1966-72, and 1973-85 for never smokers defined as of 1959, 1965, and 1972 (table 9). In particular, the relative risk for current smoking in a spouse was not increased, and

there were no trends based on the environmental tobacco smoke index.

As expected, there was a strong, positive dose-response relation between active cigarette smoking and deaths from coronary heart disease, lung cancer, and chronic obstructive pulmonary disease during 1960-98 (table 10[10]). These relative risks were consistent with those for the full CPS I cohort until 1972.[15 17] As it is generally considered that exposure to environmental tobacco smoke is roughly equivalent to smoking one cigarette per day,[4] we extrapolated the relative risk due to exposure to environmental tobacco smoke from the relative risks for smoking 1-9 cigarettes per day. These extrapolated relative risks were about 1.03 for coronary heart disease and about 1.20 for lung cancer and chronic obstructive pulmonary disease. Based on these findings, exposure to environmental tobacco smoke could not plausibly cause a 30% increase in risk of coronary heart disease in this cohort, although a 20% increase in risk of lung cancer and chronic obstructive pulmonary disease could not be ruled out.

Discussion

On the basis of our findings from the long term follow up of the California cohort of the cancer prevention study (CPS I), the association between exposure to environmental tobacco smoke and coronary heart disease and lung cancer may be considerably weaker than generally believed. Although participants in CPS I are not a representative sample of the US population, never smokers in this cohort had a total death rate that was close to that of US white never smokers.[21] Furthermore, the relative risks were based on comparisons within the cohort and should be valid. Although the participants' total exposure to smoking in a spouse was affected by the substantial extent of smoking cessation since 1959,[18] this did not affect the relative comparisons. Also, the relative risks during short follow up periods, with limited cessation, were similar to the long term risks.

Strengths of study

CPS I has several important strengths: long established value as a prospective epidemiological study, large size, extensive baseline data on smoking and potential confounders, extensive follow up data, and excellent long term follow up. None of the other cohort studies on environmental tobacco smoke has more strengths, and none has presented as many detailed results. Considering these strengths as a whole, the CPS I cohort is one of the most valuable samples for studying the relation between environmental tobacco smoke and mortality.

Concern has been expressed that smoking status of the spouse as of 1959 does not accurately reflect total exposure to environmental tobacco smoke because there was so much exposure to non-residential

Table 8 Level of smoking in spouse and deaths from selected causes among female never smokers in California cancer prevention study (CPS I) cohort, as of 1959 and 1972. For reference, 1960-98 death rate in deaths per 1000 person years adjusted to 1960 US population for attained ages 35-84 is given[16]

	All 1959 participants, followed 1960-98			1959 participants aged ≥50, followed 1960-98		Participants defined in 1972, followed 1973-98	
Smoking in spouse and cause of death	No of deaths/No of participants	Age adjusted relative risk (95% CI)	Fully adjusted relative risk (95% CI)	No of deaths/No of participants	Age adjusted relative risk (95% CI)	No of deaths/No of participants	Age adjusted relative risk (95% CI)
Coronary heart disease (death rate 1.65/1000)							
Never (1)*	1053/7399	1.00	1.00	891/4230	1.00	428/3090	1.00
Former (2)*	1059/6858	1.02 (0.93 to 1.11)	1.03 (0.94 to 1.13)	909/4424	0.98 (0.89 to 1.08)	772/5079	1.03 (0.92 to 1.16)
Current:							
Pipe or cigar (3)*	389/2691	0.99 (0.88 to 1.11)	0.97 (0.86 to 1.10)	162/1735	0.97 (0.86 to 1.10)	24/173	0.99 (0.66 to 1.49)
1-9 cigarettes/day (4)*	183/1102	1.13 (0.97 to 1.33)	1.03 (0.86 to 1.23)	162/719	1.15 (0.97 to 1.36)	24/200	0.89 (0.59 to 1.34)
10-19 cigarettes/day (5)*	310/2117	1.03 (0.91 to 1.17)	0.99 (0.86 to 1.14)	272/1301	1.03 (0.90 to 1.18)	42/344	0.90 (0.66 to 1.24)
20 cigarettes/day (6)*	412/3288	1.04 (0.92 to 1.16)	1.02 (0.90 to 1.16)	309/1735	0.96 (0.84 to 1.10)	89/616	1.30 (1.04 to 1.64)
21-39 cigarettes/day (7)*	167/1646	0.95 (0.80 to 1.12)	0.88 (0.74 to 1.06)	127/792	0.95 (0.79 to 1.15)	25/239	1.14 (0.76 to 1.71)
≥40 cigarettes/day (8)*	72/841	0.83 (0.65 to 1.06)	0.80 (0.62 to 1.03)	49/399	0.74 (0.55 to 0.98)	20/211	0.89 (0.57 to 1.40)
Total of current smokers	1533/11685	1.01 (0.93 to 1.09)	0.97 (0.89 to 1.06)	1258/6681	0.98 (0.90 to 1.07)	224/1783	1.06 (0.90 to 1.25)
Ever	2592/18543	1.01 (0.94 to 1.08)	0.99 (0.92 to 1.08)	2167/11105	0.98 (0.91 to 1.06)	996/6862	1.04 (0.93 to 1.16)
8 level index	3645/25942	1.00 (0.98 to 1.01)	0.99 (0.97 to 1.00)	3058/15335	0.99 (0.97 to 1.01)	1424/9952	1.02 (0.98 to 1.05)
Lung cancer (death rate 0.08/1000)							
Never	51	1.00	1.00	31	1.00	25	1.00
Former	51	1.08 (0.73 to 1.60)	1.04 (0.69 to 1.57)	33	1.02 (0.62 to 1.66)	39	0.92 (0.56 to 1.53)
Current	75	0.93 (0.65 to 1.33)	0.88 (0.60 to 1.28)	44	0.86 (0.54 to 1.36)	14	1.00 (0.52 to 1.92)
Ever	126	0.99 (0.72 to 1.37)	0.94 (0.66 to 1.33)	77	0.93 (0.61 to 1.41)	53	0.95 (0.59 to 1.53)
8 level index	177	0.97 (0.91 to 1.04)	0.97 (0.90 to 1.05)	108	0.98 (0.89 to 1.07)	78	0.99 (0.87 to 1.13)
Chronic obstructive pulmonary disease (death rate 0.06/1000)							
Never	45	1.00	1.00	35	1.00	21	1.00
Former	50	1.17 (0.78 to 1.75)	1.24 (0.80 to 1.93)	37	1.01 (0.64 to 1.60)	36	1.00 (0.59 to 1.72)
Current	78	1.11 (0.77 to 1.60)	1.12 (0.74 to 1.69)	54	0.94 (0.61 to 1.44)	18	1.57 (0.84 to 2.96)
Ever	128	1.13 (0.80 to 1.58)	1.16 (0.80 to 1.70)	91	0.97 (0.66 to 1.44)	54	1.14 (0.69 to 1.89)
8 level index	173	0.99 (0.92 to 1.06)	0.98 (0.91 to 1.06)	126	0.97 (0.89 to 1.06)	75	1.06 (0.94 to 1.20)

*Values in parentheses are index level of environmental tobacco smoke.

Table 9 Level of smoking in spouse and deaths from coronary heart disease among never smokers in California cancer prevention study (CPS I) cohort, as of 1959, 1965, and 1972

Smoking in spouse	1960-5		1966-72		1973-85	
	No of deaths/No of participants	Age adjusted relative risk (95% CI)	No of deaths/No of participants	Age adjusted relative risk (95% CI)	No of deaths/No of participants	Age adjusted relative risk (95% CI)
Males*:						
Never	224/7458	1.00	304/6762	1.00	769/5300	1.00
Former	7/624	0.64 (0.30 to 1.35)	19/581	1.07 (0.67 to 1.71)	47/490	0.95 (0.71 to 1.28)
Current	30/1537	1.07 (0.72 to 1.57)	36/1429	0.85 (0.60 to 1.20)	120/1185	0.97 (0.80 to 1.18)
Ever	37/2161	0.94 (0.66 to 1.34)	55/2010	0.91 (0.68 to 1.21)	167/1675	0.97 (0.82 to 1.15)
7 level index†	261/9619	1.02 (0.91 to 1.15)	359/8772	0.95 (0.86 to 1.05)	936/6975	1.01 (0.95 to 1.06)
Females*:						
Never	49/7399	1.00	124/7008	1.00	408/5343	1.00
Former	63/6858	1.26 (0.87 to 1.84)	102/6432	0.83 (0.64 to 1.08)	410/4896	1.01 (0.88 to 1.15)
Current	61/11685	1.10 (0.75 to 1.62)	141/11002	0.87 (0.68 to 1.11)	565/8433	1.02 (0.90 to 1.16)
Ever	124/18543	1.16 (0.83 to 1.61)	243/17434	0.85 (0.68 to 1.06)	975/13323	1.02 (0.90 to 1.14)
8 level index†	173/25942	1.01 (0.93 to 1.10)	367/24442	0.98 (0.92 to 1.03)	1393/18666	1.00 (0.98 to 1.03)
Males‡:						
Never			271/6173	1.00	453/3404	1.00
Former			20/726	0.87 (0.55 to 1.37)	56/573	0.93 (0.70 to 1.23)
Current			26/1053	0.79 (0.53 to 1.19)	48/525	1.00 (0.74 to 1.35)
Ever			46/1779	0.82 (0.60 to 1.13)	104/1098	0.96 (0.77 to 1.20)
7 level index†			317/8265	0.97 (0.87 to 1.08)	557/4502	1.00 (0.93 to 1.09)
Undefined after 1959			42/726		379/2473	
Females‡:						
Never			92/6138	1.00	180/3090	1.00
Former			112/9042	0.81 (0.62 to 1.07)	287/5079	0.92 (0.76 to 1.11)
Current			62/5660	0.98 (0.70 to 1.36)	81/1783	1.02 (0.78 to 1.33)
Ever			174/14702	0.86 (0.67 to 1.11)	368/6862	0.94 (0.79 to 1.13)
8 level index†			266/20840	1.00 (0.94 to 1.07)	548/9952	1.03 (0.97 to 1.09)
Undefined after 1959			101/3602		845/8714	

*Smoking in spouse defined by 1959 questionnaire.
†Index of environmental tobacco smoke based on seven or eight levels of smoking in spouse.
‡Smoking in spouse defined by 1965 questionnaire for 1966-72 and by 1972 questionnaire for 1973-85.

environmental tobacco smoke at that time.[6] The 1999 questionnaire showed that the smoking status of spouses was directly related to a history of total exposure to environmental tobacco smoke. It also showed that the extent of misclassification of exposure was not sufficient to obscure a true association between environmental tobacco smoke and coronary heart disease among women (see tables 4 and 5).

Our methodology and results are fully described because of concern that the earlier analysis of coronary heart disease in CPS I [10] was flawed by author bias owing to funding by the tobacco industry.[4] Our results for coronary heart disease and lung cancer are consistent with those of most of the other individual studies on environmental tobacco smoke,[4-8] including the results for coronary heart disease and lung cancer in the full CPS I.[10 16] Moreover, when our results are included in a meta-analysis of all results for coronary heart disease, the summary relative risks for current and ever exposure to environmental tobacco smoke are reduced to about 1.05, indicating a weak relation.

Widowhood was strongly correlated with smoking status of spouses, owing to the reduced survival of smokers. Since widowers have higher death rates than married people,[22 23] controlling for widowhood would be expected to reduce the relative risks in this and other studies of smoking in spouses. The precise effect of widowhood due to smoking in spouses still needs to be determined, but it may partially explain the positive relative risks found in other cohorts.

Conclusion

The results of the California CPS I cohort do not support a causal relation between exposure to environ-

What is already known on this topic

Exposure to environmental tobacco smoke is generally believed to increase the risk of coronary heart disease and lung cancer among never smokers by about 25%

This increased risk, based primarily on meta-analysis, is still controversial due to methodological problems

What this study adds

In a large study of Californians followed for 40 years, environmental tobacco smoke was not associated with coronary heart disease or lung cancer mortality at any level of exposure

These findings suggest that the effects of environmental tobacco smoke, particularly for coronary heart disease, are considerably smaller than generally believed

Active cigarette smoking was confirmed as a strong, dose related risk factor for coronary heart disease, lung cancer, and chronic obstructive pulmonary disease

Table 10 1960-98 age adjusted relative risk (95% confidence interval) of death for coronary heart disease, lung cancer, and chronic obstructive pulmonary disease among cigarette smokers compared with never smokers as function of active smoking status (cigarettes per day) in 1959

	Men		Women	
Active smoking status	**No of deaths/No of participants**	**Age adjusted relative risk (95% CI)**	**No of deaths/No of participants**	**Age adjusted relative risk (95% CI)**
Coronary heart disease				
Never (1)*	2561/10862	1.00	8516/39216	1.00
Former (2)*	2579/10204	1.18 (1.12 to 1.25)	541/4838	0.98 (0.90 to 1.07)
Current (cigarettes/day):				
1-9 (3)*	376/1548	1.19 (1.07 to 1.33)	590/4687	1.13 (1.04 to 1.23)
10-19 (4)*	859/3740	1.42 (1.31 to 1.53)	855/6691	1.43 (1.33 to 1.54)
20 (5)*	1661/7186	1.57 (1.48 to 1.68)	912/6875	1.79 (1.66 to 1.92)
21-39 (6)*	1072/4789	1.75 (1.63 to 1.89)	254/2066	2.04 (1.80 to 2.32)
40-80 (7)*	573/2621	1.91 (1.74 to 2.10)	111/818	2.38 (1.97 to 2.87)
Total of current smokers	4541/19884	1.53 (1.45 to 1.61)	2722/21137	1.49 (1.42 to 1.56)
7 level index	9681/40950	1.11 (1.10 to 1.12)	9804/65191	1.14 (1.13 to 1.16)
Lung cancer				
Never (1)	92/10862	1.00	269/39216	1.00
Former (2)	281/10204	3.50 (2.77 to 4.43)	48/4838	1.45 (1.06 to 1.97)
Current (cigarettes/day):				
1-9 (3)	47/1548	4.08 (2.87 to 5.80)	62/4687	1.98 (1.50 to 2.62)
10-19 (4)	187/3740	7.86 (6.11 to 10.11)	205/6691	5.07 (4.19 to 6.12)
20 (5)	535/7186	12.50 (9.99 to 15.63)	355/6875	9.14 (7.73 to 10.81)
21-39 (6)	424/4789	16.43 (12.99 to 20.77)	162/2066	15.14 (12.26 to 18.69)
40-80 (7)	241/2621	18.65 (14.47 to 24.02)	62/818	15.77 (11.80 to 21.06)
Total of current smokers	1434/19884	11.91 (9.64 to 14.73)	846/21137	6.22 (5.39 to 7.16)
7 level index	1807/40950	1.54 (1.50 to 1.58)	1163/65191	1.69 (1.63 to 1.74)
Chronic obstructive pulmonary disease				
Never (1)	103/10862	1.00	296/39216	1.00
Former (2)	179/10204	2.06 (1.62 to 2.63)	48/4838	1.42 (1.05 to 1.94)
Current (cigarettes/day)				
1-9 (3)	35/1548	2.84 (1.94 to 4.17)	50/4687	1.64 (1.21 to 2.22)
10-19 (4)	125/3740	5.46 (4.19 to 7.11)	214/6691	5.69 (4.73 to 6.85)
20 (5)	326/7186	8.30 (6.62 to 10.40)	309/6875	9.32 (7.85 to 11.06)
21-39 (6)	258/4789	11.99 (9.39 to 15.31)	106/2066	12.87 (10.13 to 16.35)
40-80 (7)	148/2621	13.54 (10.33 to 17.75)	46/818	15.33 (11.06 to 21.23)
Total of current smokers	892/19884	8.08 (6.58 to 9.94)	725/21137	5.98 (5.19 to 6.89)
7 level index	1174/40950	1.55 (1.51 to 1.60)	1069/65191	1.67 (1.62 to 1.73)

*Values in parentheses are index level of active cigarette smoking.

mental tobacco smoke and tobacco related mortality, although they do not rule out a small effect. Given the limitations of the underlying data in this and the other studies of environmental tobacco smoke and the small size of the risk, it seems premature to conclude that environmental tobacco smoke causes death from coronary heart disease and lung cancer.

We thank Lawrence Garfinkel and Clark W Heath Jr (former vice presidents for epidemiology and statistics, American Cancer Society) for facilitating the extended follow up of CPS I and for making helpful comments and suggestions and Saman Assefi and Parveen Sra for technical assistance.

Contributors: JEE conceived the study and obtained funding, conducted the extended follow up, analysed the data, and drafted the manuscript; he will act as guarantor for the paper. GCK contributed to the follow up questionnaire, advised on the data analysis and interpretation, and contributed extensively to the manuscript.

Funding: The American Cancer Society initiated CPS I in 1959, conducted follow up until 1972, and has maintained the original database. Extended follow up until 1997 was conducted at the University of California at Los Angeles with initial support from the Tobacco-Related Disease Research Program, a University of California research organisation funded by the Proposition 99 cigarette surtax (www.ucop.edu/srphome/trdrp). After continuing support from the Tobacco-Related Disease Research Program was denied, follow up through 1999 and data analysis were conducted at University of California at Los Angeles with support from the Center for Indoor Air Research, a 1988-99 research organisation that received funding primarily from US tobacco companies.[24]

Competing interests: In recent years JEE has received funds originating from the tobacco industry for his tobacco related epidemiological research because it has been impossible for him to obtain equivalent funds from other sources. GCK never received funds originating from the tobacco industry until last year, when he conducted an epidemiological review for a law firm which has several tobacco companies as clients. He has served as a consultant to the University of California at Los Angeles for this paper. JEE and GCK have no other competing interests. They are both lifelong non-smokers whose primary interest is an accurate determination of the health effects of tobacco.

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Effect of passive smoking on health

More information is available, but the controversy still persists

Papers p1057

In 1928 Schönherr proposed that lung cancers among non-smoking women could be caused by inhalation of their husbands' smoke.[1] Since then a substantial body of research has appeared, but the impact of environmental tobacco smoke on health remains under dispute.[2] The paper by Enstrom and Kabat in this week's *BMJ* will add to this debate.[3]

Given the small health risks associated with exposure to environmental tobacco smoke and thus the large study sizes required, meta-analysis has played an important part in establishing the apparent adverse health effects. A controversial issue in this regard relates to an analysis of the American Cancer Society's first cancer prevention study, funded by the tobacco industry.[4] This has not generally been included in meta-analyses, although it would contribute the largest number of events to such an analysis. The main argument advanced for not including it in meta-analyses is that the published analysis of the study was not presented in a format that allowed for the combination of equivalent effect estimates across studies.

Enstrom and Kabat have analysed the Californian subsample of the American Cancer Society's first cancer prevention study (ACSI), with considerable additional follow up, and have presented data in a format that allows inclusion in future meta-analyses. They interpret their findings as null, although, inevitably, statistical uncertainty remains. They may overemphasise the negative nature of their findings. With respect to chronic obstructive pulmonary disease—plausibly related to exposure to environmental tobacco smoke—the estimates based on the most accurately classified exposure groups give relative risks of 1.80 in men and 1.57 in women. These are said to be non-significant, but combining them—and there is no good evidence that exposure to environmental tobacco smoke has a different effect for men and women—gives a relative risk of 1.65 (95% confidence interval 1.0 to 2.73). A substantial increased risk of chronic obstructive pulmonary disease could result from exposure to environmental tobacco smoke.

Despite this it is certain that this paper will be hailed as showing that the detrimental effect of passive smoking has been overstated, and controversy will continue. What are the issues? Confounding is clearly important, and individuals exposed to environmental tobacco smoke may display adverse profiles in relation to socioeconomic position and health related behaviours. The American Cancer Society's first cancer prevention study was established in 1959, when smoking was much less associated with such factors than it currently is in the United States. It could be argued that this is why smaller risks associated with environmental tobacco smoke are seen in the first, compared to the second, American Cancer Society study (ACS II).[5] In the second study with participants recruited in 1982, women exposed to environmental tobacco smoke had less education than those unexposed,[5] as opposed to the lack of any such gradient in the first study. Similarly among men in the 1982 cohort there was little educational gradient, whereas among men in the 1959 cohort the exposed group had more education than the unexposed group. These figures reflect changing social gradients in smoking among men and women over time. Socioeconomic confounding in the second study would lead to overestimation of the effect of environmental tobacco smoke, whereas there is relatively little confounding in the first study, and what confounding there is could lead to underestimation of the effects of environmental tobacco smoke. The findings of the two studies are, in some respects, in line with this—in the second study exposure to environmental tobacco smoke was associated with increased risk of mortality due to coronary heart disease,[5] while this is not seen in the first study.[3]

Misclassification is a key issue in studies of passive smoking. It is not being married to a smoker—the indicator of exposure to environmental tobacco smoke used in the paper by Enstrom and Kabat—that leads to disease; rather, it is the inhalation of environmental tobacco smoke. As an indicator of exposure to environmental tobacco smoke the smoking status of spouses is a highly approximate measure. This will lead to the risk associated with environmental tobacco smoke being underestimated. Conversely misclassification of confounders can lead to statistical adjustment failing to account fully for confounding, leaving apparently "independent" elevated risks that are residually confounded.[6] Methods of statistically correcting for misclassification both in the exposure of interest and in confounders exist, but they are highly dependent on the validity of assessments of measurement imprecision.[6] In the field of passive smoking the tobacco industry has eagerly discussed measurement error that would lead to the effect of passive smoking being overestimated, and it relies on the work of its consultants in this regard[7] while ignoring misclassification that would lead to underestimation of the strength of the association between environmental tobacco smoke and disease.[2]

A second approach to evaluating the risks of passive smoking is to assess the exposure to known carcinogens produced by environmental tobacco smoke. Tobacco industry consultants have repeatedly said that levels of such exposures are too low to be of concern and that even a heavily exposed passive smoker inhales much less than the equivalent of one cigarette a day.[2] However, the amount of exposure to the over 4000 compounds within cigarette smoke differs between passive and active smokers, since sidestream and mainstream smoke have different compositions. Metabolites of the tobacco specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone are excreted in urine, and concentrations in non-smoking women married to smokers are about 6% of those of their spouses.[8] Given the strength of relation between active smoking and lung cancer, exposure to 6% of the dose that is received by an active smoker could easily produce the level of risk

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associated with passive smoking.[8] However, the exact factors in cigarette smoke responsible for its detrimental health consequences are not fully understood, and such calculations are approximate.

The considerable problems with measurement imprecision, confounding, and the small predicted excess risks limit the degree to which conventional observational epidemiology can address the effects of exposure to environmental tobacco smoke. Randomised controlled trials of exposure to environmental tobacco smoke will clearly not be carried out, but understanding could be improved through Mendelian randomisation.[10]

Genetic polymorphisms that are associated with poor detoxification of carcinogens in tobacco smoke have been identified. The distribution of these polymorphisms in the population will not be associated with the behavioural and socioeconomic confounders that exposure to environmental tobacco smoke is. Among people unexposed to the carcinogens in environmental tobacco smoke there is no reason to believe that the detoxification polymorphisms should be related to risk of lung cancer. However, among those exposed to environmental tobacco smoke a decrease in the ability to detoxify such carcinogens should be related to risk of lung cancer, if exposure to environmental tobacco smoke is indeed responsible for increased risk of lung cancer. One study showed that a null (non-functional) variant of one such detoxification enzyme, glutathione S-transferase M1, was associated with an increased risk of lung cancer in non-smoking women exposed to environmental tobacco smoke, but not in non-exposed non-smoking women.[11] A later study failed to confirm this finding,[12] reflecting one limitation of Mendelian randomisation, which is that large sample sizes are required to produce robust results. However, this is a promising strategy if we really want to know whether passive smoking increases the risk of various diseases.

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Competing interests: None declared.

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The therapeutic effects of meditation

The conditions treated are stress related, and the evidence is weak

Meditation includes techniques such as listening to the breath, repeating a mantra, or detaching from the thought process, to focus the attention and bring about a state of self awareness and inner calm. There are both cultic and non-cultic forms, the latter developed for clinical or research use. The relaxation and reduction of stress that are claimed to result from meditation may have prophylactic and therapeutic health benefits, and a plethora of research papers purport to show this. However, this research is fraught with methodological problems, which I outline here, along with a short summary of the best evidence for the therapeutic effects of meditation in clinical populations. There is no Cochrane review on meditation.

Showing that certain physiological effects such as a slowed heart rate or a particular electroencephalographic pattern occur during meditation and characterise a "relaxed state" may give insight into how meditation works but does not prove its therapeutic value. Most trials of the cumulative effects of meditation have had weak designs. Trials of transcendental meditation (a popular form of mantra meditation), when controlled at all, often compared self selected meditators with non-meditators or long term meditators with novices. These trials did not control for systematic differences between people who elect to learn the technique and those who do not, and between people who persist with the practice and those who abandon it. Randomised trials have often recruited favourably predisposed subjects so that expectations of benefit differ from control subjects. In trials of transcendental meditation for cognitive effects I found that positive outcome was confined to trials with subjects so recruited and to trials with passive controls such as "eyes closed rest." Trials with naive subjects and plausible controls (for example, pseudo-meditation) were negative. A similar association was previously found in a meta-analysis of cognitive behavioural techniques (including meditation) for hypertension.[1] Other weaknesses have been use of multiple co-interventions, high attrition, and inadequate statistical analysis. Recent trials in clinical

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From hero to pariah in one easy jump

18 May 2003

Richard Smith,
Editor
BMJ

Send response to journal:
Re: From hero to pariah in one easy jump

Email Richard Smith:
rsmith@bmj.com

Not long ago I was something of a hero of the antitobacco movement-- because I resigned my professorship at Nottingham University when it accepted money from British American Tobacco. I felt somewhat embarrassed by the whole episode. I was no hero. But now I'm a pariah for publishing a piece of research funded by the tobacco industry. Because of some sort of personality defect that is common among editors I'm more attracted to being a pariah than a hero, but I don't think that I deserve to be a pariah.

We long ago decided that we would not have a blanket policy of refusing to publish research funded by the tobacco industry, as some journals have done. (1) Our argument was that a ban would be antiscience, systematically distorting the scientific record.

I would try to dissuade anybody from accepting tobacco company money, and I resigned from Nottingham because it did so. Isn't it thus hypocritical to publish research funded by the industry? To my mind it isn't. With some difficulty, I'm setting the ethic that all science should be published above the ethic that you shouldn't take money from the tobacco industry. Once the research has been done it should be published, and if it passes our peer review process it can be published in the BMJ.

Our way of making decision on research papers is first to ask if we are interested in the question. We are certainly interested in the question of whether passive smoking kills, and it's clear to us that the question has not been definitively answered. Indeed, it may well never be answered definitively. It's a hard question, and our methods are inadequate. We then peer review the study. Two top epidemiologists-- including George Davey Smith-- reviewed the paper. Then the paper went to our hanging committee, which always includes a statistician as well as practising doctors and some of us. Everybody reads every word of every paper. We asked for extensive changes to the paper, and the paper we published was different from the paper submitted--which is usually the case.

We are planning to post on our website all the comments of the reviewers, our statistician, and the hanging committee. I hope that they will be up soon after the weekend.

Of course the paper has flaws --all papers do-- but it also has considerable strengths-- long follow up, large sample size, and more complete follow up than many such studies. I find it disturbing that so many people and organisatons --including the BMA, our owners-- refer to the flaws in the study without specifying what they are.

We judged this paper to be a useful contribution to an important debate. We may be wrong, as we are with many papers. That's science. But I remain convinced that it would have been wrong to reject the study simply because it was funded by the tobacco industry.

Richard Smith Editor, BMJ

(1) Roberts J, Smith R. Publishing research supported by the tobacco industry. BMJ 1996; 312: 133-134.

Competing interests: I'm the editor of the BMJ and acountable for all that it publishes.

Warning: the health police can seriously addle your brain

By Robert Matthews

(Filed: 18/05/2003)

It was a rare good news story in an otherwise grim week. A landmark study into the effects of inhaling other people's smoke revealed that fears that passive smoking kills more than 1,000 a year in the UK alone are unfounded.

After studying the health of tens of thousands of people married to smokers, US researchers found that they face no significant extra risk of lung cancer or heart disease. It may sting your eyes, take your breath away and make your clothes smell, but other people's cigarette smoke will not kill you.

The demise of a supposed major risk to public health might be expected to prompt celebration among medical experts and campaigners. Instead, they scrambled to condemn the study, its authors, its conclusions, and the journal that published them. The reaction came as no surprise to those who have tried to uncover the facts about passive smoking. More than any other health debate, the question of whether smokers kill others as well as themselves is engulfed in a smog of political correctness and dubious science.

Researchers who dissent from the party line face character assassination and the termination of grants. Those who report their findings are vilified as lackeys of the tobacco industry, and accused of professional misconduct (in 1998, campaigners tried to have this newspaper censured by the Press Complaints Commission for our reports on passive smoking. They failed.).

The furore over last week's negative findings, reported in the respected British Medical Journal, has its origins in research published in the same journal in October 1997. After reviewing the evidence from dozens of studies, researchers at the Wolfson Institute of Preventive Medicine, London, concluded that being married to a smoker increases the "risk" of lung cancer and heart disease by around 25 per cent.

The results were seized on by health campaigners as final proof of what they had known all along: that smokers are not just killing themselves - they are also killing innocent bystanders, and must be stopped. The same issue of the BMJ carried an editorial by Dr Ronald Davis, the editor of the journal Tobacco Control, declaring: "Health advocates should pursue all strategies that would help accomplish that goal, including education, legislation, regulation and litigation."

Just how willing campaigners are to pursue all strategies soon became clear. In March 1998, The Telegraph revealed that an international study by the World Health Organisation had failed to find any convincing evidence of a link between passive smoking and cancer. The article prompted uproar among anti-smoking campaigners and denials from the WHO, which insisted that the study had found a 16 per cent increase in cancer "risk" among those married to smokers.

The WHO, in what has become a standard ruse in the passive smoking debate, ignored the fact that the 16 per cent risk figure was not "statistically significant". That is, it had failed to meet the standard of proof usually demanded by scientists.

As The Telegraph has discovered, however, passive smoking research is an area where the usual standards do not apply. If they did, last week's wholly negative findings would have surprised no one. For long before the publication of the original BMJ studies, it had been clear that the 25 per cent extra risk figure was likely to prove a wild exaggeration.

The evidence comes from research into a key issue in the passive smoking debate: just how much smoke do non-smokers actually inhale? Surprisingly few attempts have been made to gauge smoke exposure directly. Those that have raise grave doubts over claims that passive smoking poses a significant health risk.

In studies across Europe over the past decade, air quality experts at Covance Laboratories, Harrogate, gave air monitors to thousands of people and measured their exposure to smoke. The startling results showed that passive smokers are exposed to the equivalent of six cigarettes a year, an extra lung cancer risk of 2 per cent compared with non-smokers. The figure is 10 times lower than the BMJ studies claimed.

So small a risk is, however, in line with last week's negative findings. It also explains an awkward fact rarely mentioned by anti-smoking campaigners: more than 80 per cent of all studies of passive smoking have failed to find a statistically

significant link to lung cancer. Only by subjecting them to abstruse statistical techniques can they deliver the goods.

One technique is anything but abstruse, however. It involves simply ignoring results that do not fit. In the original BMJ reports, a major US study showing no extra heart disease risk from passive smoking was excluded on the grounds that it did not fit with the positive results, and had been funded by the tobacco industry. The air monitoring studies have been ignored for the same reasons.

Scientists are understandably chary of research backed by an industry with a history of deceit. Yet so widespread is the conviction that passive smoking is a proven killer that researchers who think otherwise have little choice but to apply for tobacco industry support. Prof James Enstrom, of the University of California, the lead author of the study whose negative findings sparked last week's controversy, said the research would never have seen the light of day, except for support from the tobacco industry.

Originally set up in 1959 by the American Cancer Society, who recruited 118,000 Californian adults into the study, the follow-up effort was long supported by taxes levied on cigarettes. In 1997 the funding was suddenly cut off. Prof Enstrom suspects that health officials in California just were not keen to fund research that might undermine the original BMJ studies.

Prof Enstrom, compelled to take tobacco industry money to complete the study, then found that journals were unwilling to publish his negative findings. He told The Telegraph: "One journal we tried had published three positive studies before, but despite getting a glowing referee's report on our work, they refused to accept it."

After the BMJ published it last week, he has been subjected to a barrage of criticism: "The whole process has been aggressive, vitriolic hate," he says.

Within hours of publication, he and his co-author Dr Geoffrey Kabat, of the State University of New York, came under attack by the very organisation that had set up his study: the American Cancer Society. "We are appalled that the tobacco industry has succeeded in giving visibility to a study with so many problems," said a spokesman, adding that the study was "neither reliable nor independent".

But, Prof Enstrom said, the speed of the society's response to the negative findings is particularly revealing. "They wrote the complaint before they even saw the paper," he said.

In the UK, the anti-smoking pressure group Ash accused Prof Enstrom and his colleague of "deliberately downplaying the findings to suit their tobacco paymasters". But Prof Enstrom says they were subjected to rigorous peer review, and denies tobacco industry influence.

The denial appears to have satisfied the BMJ. Dr Richard Smith, the journal's editor, told The Telegraph that the decision to publish the findings was made only after they had been thoroughly refereed, and full disclosure made of the source of funding. "This is a big study with very complete follow-up about an important question," Dr Smith said. "I take the view that not to publish is a form of scientific misconduct."

Now Dr Smith, too, is under fire from his own colleagues. Dr Vivienne Nathanson, the head of science and ethics at the British Medical Association, said: "There is decades of overwhelming evidence that passive smoking causes lung cancer and heart disease, as well as triggering asthma attacks."

The reference to asthma hints at a new strategy by anti-smoking campaigners - towards a focus on the health of children. Unlike the risks from lung cancer and heart disease, the evidence that passive smoking damages the lungs of children is strong. Last week the British Thoracic Society called for more funding into this aspect of the smoking and health debate. That suggests that children with disorders such as asthma may soon become the focus of attempts to introduce a total ban on smoking in public places.

In the meantime, health campaigners show no enthusiasm for giving up their most potent claim: that the person puffing away next to you is not merely making your eyes water, but killing you as well. The scientific evidence is just not there, says Prof Enstrom. "But maybe we've gone past the point where anyone cares about the facts."

Français à la page suivante

Polemic and public health

Lewis Lapham, editor of *Harper's Magazine*, recently paused in his monthly diatribe against US foreign policy to lampoon a more local target: the use of public-smoking prohibitions in New York City to root out the evils of second-hand smoke. In Lapham's view, these attempts at "social hygiene," which threaten to extend as far as a ban on smoking in public parks, are an irrational assault on personal liberty, fuelled by exaggerated fears of risk. "Statistics," writes this smoker of 50 years, "can be made to fit any season's fashions."[1]

A skeptical view of the risks of second-hand smoke also arose recently from a less polemical source: in May, *BMJ* published a study based on observations obtained over 39 years on 35 561 adults who had never smoked and whose spouses' smoking habits were known. The authors found "no significant associations" between tobacco-related mortality and exposure to second-hand smoke.[2] The journal's editors offered a blunt provocation to political correctness by stating on the front cover: "Passive smoking may not kill." Predictably, the study and its declared tobacco-industry sponsorship caused a furor.

In trying to understand the risks posed to human health by environmental contaminants, we have a limited range of research methodologies at our disposal. We cannot do randomized trials to test the effects of smoking, lead poisoning or the use of cell phones in cars. We're stuck with observational studies: always messy, confounded, susceptible to passion and open to dispute.

The problem with the data on passive smoking (and many other potential environmental hazards) is that the estimated risks are so close to zero. The study published in *BMJ* showed that the risks of heart disease, lung cancer and chronic obstructive pulmonary disease among never-smokers living with a smoker compared to never-smokers living with a nonsmoker were 0.94 (95% confidence interval [CI] 0.85–1.05), 0.75 (95% CI 0.42–1.35) and 1.27 (95% CI 0.78–2.08) respectively — all statistically insignificant and none very large.

Fifty-three years ago *BMJ* published research by Doll and Hill on 649 men who had lung cancer and compared their smoking habits with a group of 649 comparable men who did not have lung cancer.[3] The risk (odds ratio) of lung cancer among smokers compared to nonsmokers was 14.0, meaning that smokers were 14 times more likely to develop lung cancer than nonsmokers.

This result is interesting for 3 reasons. First, it is instructive that this huge increase in risk was not apparent from casual observation: because most men smoked, the effects of this behaviour were inapparent. Second, although even these astonishingly high risks were disputed, this study (and others that followed) marked the start of a long but steady decline in smoking among men, followed decades later by a decline in deaths from lung cancer. Third, from the perspective of almost all current research on environmental hazards, in which odds ratios of 1.2 (or an increase of risk of 20%) are considered sufficient to prompt action by public health advocates (or social hygienists?), perhaps we should ask if we are sometimes overzealous in our attempts to publicize and regulate small hazards.

It is impossible to control completely for confounding variables in observational studies. The smaller the risk estimate, the greater the chance that confounding factors will distort it and invalidate it. This is not to say that observational studies should be abandoned. Faced with the results of the recent study we can, as individuals, elect to change our behaviours and possibly our risk exposures. But, when interpreting the results and then championing public policy and legislation to regulate exposure, we must be doubly wary of tailoring statistics to fit the current fashion. We must be open with our doubts, honest in our interpretations and cautious in our recommendations. Exaggerated claims of risk will only erode the credibility and effectiveness of public health. — *CMAJ*

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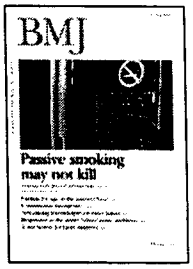
Letters



Passive smoking

Study was flawed from outset

EDITOR—The study by Enstrom and Kabat has a major flaw,[1] and I urge the editors of the *BMJ* to consider a retraction. The study assumes a considerable difference in the exposure to environmental tobacco smoke of never smokers' spouses compared to ever smokers' spouses. This is obviously wrong.

Most never smokers' spouses would have been exposed to considerable environmental tobacco smoke before the late 1990s when Californian public places became smoke-free. Thus for most of the study period, assuming the spouses are together for two to four waking hours a day, the comparison is eight to10 hours' exposure to tobacco smoke among spouses of never smokers and 12 hours' exposure to tobacco smoke among spouses of ever smokers. Assuming passive smoking increases mortality by 30%, the demonstrable difference between the groups would be about 5% ((12 – 10)/12)×30). This would be further reduced because of quitters among ever smokers and occasional smokers among never smokers. A 5% difference is extremely difficult to show in an epidemiological study, and inability to find a difference cannot be taken as absence of a difference.

However flawed this study, unless it is retracted by the *BMJ* the tobacco industry will use it to promote their vigorous opposition to antismoking legislation in general, and anti-environmental tobacco smoke laws in particular, creating controversy where there isn't any. Of course they have an urgent and ongoing need to replace loss of their customer base—10 000-20 000 lives per day—with new recruits of young smokers.

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1 Enstrom JE, Kabat, GC. Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98. *BMJ* 2003;326:1057. (17 May.)

Wider evidence needs to be interpreted

EDITOR—Enstrom and Kabat's analysis has several omissions.[1] First they accept that most epidemiological studies have found positive but not statistically significant relationships between environmental tobacco smoke, coronary heart disease, and lung cancer, but then argue against meta-analysis to establish a causal relation. This is precisely where systematic reviews, and sometimes meta-analysis, show considerable benefit by increasing power. Enstrom and Kabat say that publication bias may explain positive results in reviews; however, larger cohort studies, unlike small trials and reports, are more likely to be published, regardless of results.[2] They do not explain heterogeneity between their findings and others, simply arguing that their cohort is large, and has more strengths. In fact, large prospective cohort studies like this may have greater losses to follow up, or more misclassification, over time.[3]

Misclassification, mentioned by the authors, may explain the apparent lack of association. Furthermore, the relative risks reported for active smoking and coronary heart disease (relative risk 1.5, table 10 in the paper) are lower than other cohort studies, which may be sufficient to obscure a modest but important increase in risk.[4,5] They further assume an (unlikely) linear relation between cigarette smoking and mortality to validate their main results (extrapolating a very low estimate of a relative risk of 1.03 for coronary heart disease, by implying that environmental tobacco smoke is equivalent to smoking one cigarette per day). This analysis is unclear and unconvincing.

One study is insufficient to overturn established relations between environmental tobacco smoke and mortality, and I think that the authors overemphasise their negative findings.

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Paper does not diminish conclusion of previous reports

EDITOR—I am writing on behalf of members of the 2002 working group on involuntary smoking and cancer for the International Agency for Research on Cancer (IARC).[1] We concluded that environmental tobacco smoke causes lung cancer among never smokers. The paper by Enstrom and Kabat[2] does not diminish this conclusion or those of previous reports.[3–5]

Enstrom and Kabat's paper was based on one of the 25 US states (California) in the American Cancer Society's prevention study. The relative risk of lung cancer in never smoking women married to ever smokers was reported as 0.99 (95% confidence interval 0.72 to 1.37), based on only 177 cases, whereas the IARC meta-analysis, based on 46 studies and 6257 cases, yielded an estimate of 1.24 (95% confidence interval 1.14 to 1.34).[1] The estimate of Enstrom and Kabat is consistent with both an increased risk of lung cancer (the confidence interval includes the IARC estimate of 1.24) and no effect. Adding the result from Enstrom and Kabat to the IARC analysis reduces the pooled estimate to 1.23.

The observed relative risk of 0.99 is based on the smoking status of husbands in 1959, but many would have quit by 1998, particularly in California. Table 8 in the paper confirms this; in 1959 63% of ever smoking husbands were current smokers compared with 26% in 1998. This exposure misclassification would mask the association between exposure to environmental tobacco smoke and lung cancer.

IARC's classification of environmental tobacco smoke as a human carcinogen was based on the full scope of evidence; observational studies, carcinogenic components of environmental tobacco smoke, experimental models, and biomarker studies. Additionally, active smoking is an established cause of lung cancer, and knowledge of mechanisms of carcinogenesis implies no risk free level of exposure to tobacco smoke. Enstrom and Kabat's conclusions are not supported by the weak evidence they offer, and, although the accompanying editorial alluded to "debate" and "controversy," we judge the issue to be resolved scientifically, even though the "debate" is cynically continued by the tobacco industry.

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Members of the IARC Working group: Patricia Buffler (USA), Richard Doll (UK), Elizabeth Fontham (USA), Yu-Tang Gao (China), Prakash Gupta (India), Allan Hackshaw (UK), Elena Matos (Argentina), Jonathon Samet (USA), Michael Thun (USA), Kurt Straif (France), Paolo Vineis (Italy), H-Erich Wichmann (Germany), Anna Wu (USA), David Zaridze (Russia).

Inverse correlation of smoking and education should have raised suspicion

EDITOR—It is well known that smoking is inversely correlated with education level; the highest percentage of smokers is found among those people who have not completed high school. This inverse correlation of smoking and education has been true for many years. It is referred to in the 15th edition (1977-9) of the *Encyclopedia Britannica.* Clearly, this casts suspicion on the data entry and the programming used by Enstrom and Kabat to perform their analysis,[1] because they find that the highest frequency of smoking is associated with the highest level of education.

From their table 2 (male never smokers) and table 3 (female never smokers) sorted by smoking status of spouse, they show that the heaviest smokers (≥ 40 cigarettes/day) are more likely to have completed high school than are non-smokers. Further, among smokers, they show that for those smoking a higher number of cigarettes the likelihood of completing high school is greater.

Because the "never smoked/formerly smoked" group does not show the expected higher proportion of high school graduates, this implies that there were a sizeable number of smokers included among the non-smokers; that would account for the spouses of "non-smokers" not exhibiting a lower rate of heart disease.

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Secondhand smoke does cause respiratory disease

EDITOR—The report by Enstrom and Kabat confirms that exposure to secondhand smoke causes injury to the respiratory system with the finding of a combined increased mortality risk for men and women for chronic obstructive pulmonary disease (relative risk 1.65, 95% confidence interval 1.0 to 2.73).[1] This is consistent with other investigations that show the sensitivity of the respiratory system to secondhand smoke at all ages and in different settings. In Hong Kong several studies have shown that the exposure of infants to secondhand smoke in utero or postnatally in the home was linked to higher consultation rates and hospitalisation for respiratory and other illnesses.[2] Smoking in the home was clearly associated with bronchitic symptoms in a cohort of primary school children, independently of ambient air pollution.[3] In an adult workforce, workplace exposures to passive smoking were associated with significant excess risks (66% to 212%) for all respiratory symptoms and increased healthcare costs.[4] In a population survey the prevalence of secondhand smoke exposures at work was 47.5% among non-smoking full time workers compared with only 26% at home. People exposed at work were 37% more likely to consult a doctor for respiratory illness. The increased healthcare costs for primary care alone among three million workers was estimated at US$29m (£18m; €26m) annually.[5] Four independent case control studies on lung cancer and passive smoking in Hong Kong, reviewed by the United States Environmental Protection Agency, gave an overall relative risk of 1.48 (1.21 to 1.81).

In other words, we have epidemics of respiratory disease in Hong Kong caused by secondhand smoke. However, because of the way in which the Enstrom and Kabat paper was presented little or no attention will be paid in media reports to the findings on mortality risks from respiratory disease.

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Competing interests: AJH is a former chairman of the Hong Kong Council on Smoking and Health (COSH). THL is current vice chairman of COSH. All of the authors conduct research on the health effects of active and passive smoking and have received research funds, through their employer, the University of Hong Kong, to support their work.

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Doubts about effectiveness of age adjustment

EDITOR—According to Enstrom and Kabat's figures the greater had been a man's cigarette consumption in 1959 the less likely, it seems, was the death of his wife from coronary heart disease.[1] However, an age bias existed in those women at the outset. In 1959 their mean age decreased with spousal smoking, such that the wives of men smoking 40 a day were a mean four years younger than wives of men smoking one to 19 a day, probably as a consequence of early death of smoking husbands of similarly aged wives (table 3 on bmj.com).

During the study period mortality from coronary heart disease fell by about 15% every four years.[2] The "passive" smokers were therefore predominantly from later cohorts for whom, age for age, mortality from coronary heart disease had fallen significantly in comparison to controls. The same argument applies to never smoking husbands of smoking women who had an average age four to five years lower than controls (table 2 on bmj.com). Adjusting for age alone will not remove this interaction of age and time of observation.

Moreover, the Cox proportional hazard model is critically dependent on assumed proportionality between two survival curves at all points following entry to the study.[3] Mortality from coronary heart disease increases almost exponentially for most of adult life and the mortality curves of risk groups for coronary heart disease differ not only in scale but also in doubling time. As such their survival curves cannot be proportional, yet this was not tested.

The effectiveness of age adjustment in this study is questionable, the year of observation should have been taken into account, and the statistical method is potentially unsound. The biological implausibility of the trend in relative risk may well be an expression of systematic bias in the method.

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Tobacco industry publishes disinformation

EDITOR—The American Cancer Society does not agree with the conclusions of Enstrom and Kabat in their analysis of environmental tobacco smoke in the cancer prevention study I (CPS-I).[1] Their study is fatally flawed because of misclassification of exposure. The cancer prevention study was started by the society in 1959 to measure the effects of active smoking, not to collect valid estimates of exposure to environmental tobacco smoke.[2] No information was obtained on sources of exposure to environmental tobacco smoke other than the smoking status of the spouse. Tobacco smoke was so pervasive in the United States in the 1950s and 1960s that virtually everyone was exposed, at home, at work, or in other

settings. Enstrom and Kabat essentially compare non-smokers, married to a smoking spouse, with non-smokers with other sources of exposure to environmental tobacco smoke. Misclassification of exposure is compounded because no information was collected on the smoking status of the spouse between 1972 and 1999. Non-smokers whose spouses reported smoking at the start of the study are classified as "exposed" even if the spouse quit, died, or the marriage ended during this interval. This problem is not solved by the 1999 resurvey of survivors, since these represent only 2% of the original analytic cohort and 5% of those followed after 1972. Other serious flaws of the Enstrom and Kabat paper are discussed elsewhere.[3]

This is the second attempt by tobacco industry consultants to publish flawed analyses of environmental tobacco smoke using cohort studies from the American Cancer Society.[4] Sadly, the forum in which such studies are influential is not the scientific world—scientists recognise these studies for what they are—but in communities that are considering clean air laws.

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Competing interests: None declared.

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Peer review and press release

EDITOR—The questions raised about the validity of the data reported by Enstrom and Kabat call into question the adequacy of the peer and editorial review of the paper at the *BMJ*.[1] Apparently no one with special expertise in research on the health effects of passive smoking was involved in the review of this paper. In an area as complex as this—to which massive reports have been devoted[2 3]—one or more persons with epidemiological expertise and an extensive knowledge of the literature on this subject should have been involved in the review of this paper. The obligation to find such a reviewer is heightened when one considers the authors' conflicts of interest and the fact that the paper challenges a huge body of evidence in an area of enormous public health importance.

The *BMJ*'s press release for this paper looks as if it was written by the tobacco industry. It refers to the "already controversial debate on the health impact of passive smoking" and mostly parrots the views of Enstrom and Kabat. In its eight paragraphs, the release allocates three words to the study's limitations. The coup de grâce is that the release does not mention the authors' conflicts of interest. This problem is not unique to the *BMJ*. An analysis of press releases issued by seven medical journals (including the *BMJ*) included 23 studies that were industry funded; only 22% of the corresponding press releases revealed the source of funding.[4]

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Competing interests: RMD has been active in tobacco research and tobacco control advocacy since 1979. From 1991 to 1998, he was editor of the journal *Tobacco Control*, which is published by the BMJ Publishing Group. He served as North American editor of the *BMJ* from 1998 to 2001. He has served as an expert witness in many tobacco related lawsuits (including two devoted to passive smoking) but has derived no personal income from such work (fees for his services have been paid to his employer, as he is a salaried employee).

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Agreeing the limits of conflicts of interest

EDITOR—The paper by Enstrom and Kabat[1] raises the issue of how much conflict of interest can editors reasonably allow before the findings and interpretation of a particular study are rendered unsafe or, at the very least, too uncertain to be a substantive scientific contribution?

If we think that there really is a limit to the degree of conflict that we judge reasonable, as some responses to the Enstrom and Kabat paper seem to imply, then criticism should be directed to the medical community for having such imprecise thinking over conflicts of interest. In pharma sponsored studies, we mostly allow conflicts provided they are reported accurately. We deplore them in tobacco sponsored research. But there are many examples of how both industries have tried to undermine the independence and rigour of research, bias policy makers, and gouge huge profit from disease.

In papers from the pharma industry we publish a statement about the role of the funding source in the design, conduct, analysis, and reporting of the data for all primary research, irrespective of who the sponsor might be (for-profit, not-for-profit etc). No such statement appears in the Enstrom and Kabat paper—would this have helped readers judge the safety and reliability of their research?

Could this paper therefore provide a useful opportunity for us all to clarify what is an acceptable conflict, for readers, researchers, and editors alike, and how that conflict should be reported? Could we agree also about how to handle these matters during prepublication peer review (should the extent of the conflict be a factor, in addition to the science, in deciding acceptance or rejection?)—well before they might confuse an already difficult scientific issue of great public concern?

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Background must be examined

EDITOR—The reviews of the paper by Enstrom and Kabat and the responses to them raise serious concerns about this paper,[1] strengthened by what has since emerged about one of the author's links to the tobacco industry. As an editor who has been misled by an ostensibly independent scientist later found to be a consultant for the tobacco industry, I am hesitant to criticise others who may find themselves in a potentially similar position as discovering the full story can be lengthy and painful.[2] One must consider not just the scientific merits of what was published but also the many analyses that could be but were not. One must also scrutinise carefully statements that could be genuine differences of interpretation but may reflect other motives. Especially where passive smoking is concerned, it is essential to examine the background to the study, given the unprecedented resources used by the tobacco industry in their attempts to create uncertainty.[3]

What should happen now? The *BMJ* often responds to controversial papers by simply counting responses for and against. This is insufficient, given the many unanswered questions raised by industry documents about the part played by senior tobacco industry executives and their consultants in this paper.[4] When faced with similar questions about a paper we published on passive smoking we undertook a full investigation, producing evidence that was subsequently used successfully in a legal action in Switzerland.[5] Without prejudging the outcome, such a review would, prima facie, also seem to be justified in this case.

Competing interests: See reference 4.

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Authors' reply

EDITOR—Owing to the charged atmosphere surrounding the issue of passive smoking, our paper provoked strong reactions on bmj.com. The most disturbing reactions have come from the enforcers of political correctness who pose as disinterested scientists but are willing to use base means to trash a study whose results they dislike. They have no qualms about engaging in personal attacks and unfounded insinuations of dishonesty rather than judging research on its merits.[1] The resulting confusion has misled many readers and diverted attention from the facts of the study.

Since 15 May Michael Thun of the American Cancer Society has led a campaign to discredit our study, including his letter above. However, almost every sentence in his letter is misleading, and he disregards key information in the full version of our paper. Contrary to the title of his letter, we have presented an accurate analysis of the California cohort of the cancer prevention study I (CPS I), not disinformation, and it comes from the University of California, Los Angeles, and the State University of New York, Stony Brook, not the tobacco industry.

Anyone who reads the full version of the paper and our response to the reviewers of 9 January[2] will see that in fact we provided detailed evidence that refutes the claim that our study is "fatally flawed because of misclassification of exposure." Contrary to Thun's unsubstantiated assertion that "tobacco smoke was so pervasive in the United States in the 1950s and 1960s that virtually everyone was exposed, at home, work, or in other settings," the table shows that most female never smokers married to never smokers were not exposed. It also shows that 1959 spousal smoking was strongly related to self reported total exposure to environmental tobacco smoke as of 1999, in spite of the misclassification of exposure that occurred over 40 years.

Thun also attempts to minimise our recontact of survivors in 1999. Instead of the 2% and 5% he cites, we obtained 1999 responses from 8.7% (3094/35561) of the subjects alive on 1 January 1960, from 35.6% (3094/8693) of the subjects known to be alive as of 31 December 1998, and from about 45% of the subjects who actually received the questionnaire (see table 1 and text of full paper). In addition, we have shown in tables 2 and 3 that the 1999 respondents were reasonably representative of the 1959 subjects. Thun claims that "misclassification of exposure is compounded because no information was collected on the smoking status of the spouse between 1972 and 1999," but he completely ignores table 9. This table clearly shows that results for coronary heart disease for follow up periods of 6, 7, and 13 years, when exposure misclassification would be minimised, were the same as the results in tables 7 and 8 for follow-up periods of 26 and 39 years.

Furthermore, although Thun is in a position to check our results by analysing the data from CPS I, he has yet to identify a single error. His attack should be seen for what it is—an attempt to discredit work that is at variance with the position he is committed to. However, the evidence for the health effects of passive smoking is neither as consistent nor as iron clad as Thun wants to portray it. Rather, the widely accepted evidence is the result of selective reporting of data and, when necessary, attempts to suppress divergent data. Our paper provides a prime example of these tactics.

Horton has posed serious questions regarding the issues of conflict of interest and the difficulty of determining the credibility of research findings, particularly those that involve tobacco industry funding. We suggest four things be done for controversial papers such as ours. Firstly, the integrity of the authors should be thoroughly and fairly investigated. In our case, we both have a substantial record of accomplishment in conducting relevant epidemiologic studies and, until now, we have never had our professional integrity challenged. Secondly, full disclosure should be made regarding conflicts of interest, as has been done with our paper. We want to make clear that the tobacco industry played no part in our paper other than providing the final portion of the funding. The tobacco industry never saw any version of our paper before it was published, never attempted to influence the writing of the paper in any way, and did not even know the paper was being published until it became public. In addition, we have never testified on behalf of the tobacco industry, never owned any stock in the tobacco industry, never been employees of the tobacco industry, and would never have accepted tobacco industry funds if there had been any other way to conduct this study. However, full disclosure must be required of all authors and organisations. In particular, what are the competing interests of Thun, and where does the American Cancer Society get its funds? Thirdly, and most importantly, the integrity of the underlying data must be thoroughly and fairly investigated. The best way to resolve questions about the validity of research findings is through independent examination of the underlying data, something that is now required in principle by the Data Quality Act for US studies with public policy implications.[3] Fourthly, journals must be willing to publish and discuss controversial findings, as long as they meet the criteria of good science.

Regarding the comments of the working group of the International Agency for Research on Cancer (IARC), we have not claimed that our study changes the weight of the worldwide evidence on environmental tobacco smoke and lung cancer, but it does change the US evidence. When our results are included, meta-analysis of US results on environmental tobacco smoke and lung cancer among both men and women yields a summary relative risk of about 1.10 for ever/never exposure, which is just on the border of statistical significance. Our results have an even greater impact with regard to environmental tobacco smoke and coronary heart disease, where meta-analysis of US results, which constititute most of the evidence, yields summary relative risks of about 1.05 for current/never and ever/never exposure. The end of our response to the reviewers summarises the relative risks for environmental tobacco smoke and coronary heart disease by exposure status for all US cohort studies.[2] Because of our findings, we conclude that "the association between exposure to environmental tobacco smoke and coronary heart disease and lung cancer may be considerably weaker than generally believed." Finally, we do not think the weak association with lung cancer means that environmental tobacco smoke "causes" lung cancer, and we certainly do not think that this issue is "resolved scientifically."

In response to Glaser and Milne, we have used a standard method of analysis for prospective cohort data: Cox proportional hazards regression based on the SAS PHREG program.[4] All results have been properly adjusted for age at entry, which is by far the strongest risk factor for death. Tables 7 and 8 show that confounding variables such as education have virtually no effect on the relative risks. Too much is being made of statistical fluctuations in tables 2 and 3. For a fair evaluation of our study, it must be put in perspective with all other similar studies, which has not yet been done.

Finally, we too are in favour of the strongest possible protections for nonsmokers. However, the attempt to suppress any divergent results because of their possible effect on public policy can only harm science in the long run. In a rational society, there are ample grounds for regulating involuntary exposure to tobacco smoke without manipulating scientific results. What is most dangerous is the willingness to

Self reported total exposure to environmental tobacco smoke among female never smokers in the California cohort of the cancer prevention study I by smoking status of spouse (taken mainly from tables 4 and 5 of full paper)

	History of regular exposure to cigarette smoke from others in work or daily life as of 1999 (%)			
Smoking status of spouse	None	Light	Moderate	Heavy
Low exposure:				
Married to a never smoker as of 1959	61.7	24.3	10.9	3.1
Married to a never smoker as of 1972	63.6	23.9	9.7	2.8
Never married to a smoker as of 1999	76.7	16.1	5.3	1.9
High exposure:				
Married to a smoker of 40+ cigarettes per day as of 1959	16.2	12.5	47.5	23.8
Exposed 40+ years to a smoking spouse as of 1999	14.1	20.5	44.3	21.1

distort the truth to defend one's position, claiming all along that science and righteousness are on one's side.

James E Enstrom *researcher*
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1 Rothman KJ. Conflict of interest: the new McCarthyism in science. *JAMA* 1993;269:2782-4.
2 Enstrom JE, Kabat GC. Response to BMJ/2002/011163 Manuscript Decision. *BMJ* 2003. bmj.com/cgi/content/full/326/7398/1057/DC1/7 (accessed 16 Aug 2003).
3 Data Quality Act and OMB Guidelines. Guidelines for ensuring and maximizing the quality, objectivity, utility, and integrity of information disseminated by federal agencies; notice; republication. *Federal Register* 2002;67(36):8451-60. (Friday, 22 February.) www.isrl.uiuc.edu/qrd/iq/public/data-quality-guidelines.html (accessed 16 Aug 2003).
4 So Y. The PHREG procedure. In: *SAS/STAT software. SAS technical report P-229*. Cary, NC: SAS Institute, 1992. support.sas.com/documentation/onlinedoc/index.html (accessed 19 Aug 2003).

bmj.com

Summary of rapid responses

EDITOR—More than 140 readers responded to Enstrom and Kabat's paper and Davey Smith's editorial.[1 2] Some of the passion and most of the science is captured in the letters above. What follows is a necessarily brief overview of the remaining ones. The debate started with some orthodox critical comment on the paper: the analysis underestimated the risk to passive smokers, was underpowered, distorted, poorly reported, placed out of context, or just plain wrong. The two main contentions were that a smoking spouse is a poor proxy for passive smoking (because everyone smoked in the 1950s, so people with non-smoking spouses were still exposed at work), and that many quitters are misclassified as smokers. Both would reduce the difference in mortality between exposed and non-exposed groups. In general, the criticisms were poorly substantiated; only four letters (3%) referred to actual data in the paper.

The discussions then widened to a number of more or less polite exchanges starting with the evils of the tobacco industry (too numerous to be repeated here), and the competing evils of drug companies that make nicotine replacement therapy. Neither side expressed their own view. Many readers were angry with the *BMJ* for publishing this study. More were angry about the "tabloid" cover on the journal, and the press release, which they said was sensational and misleading. Some thought the *BMJ*'s editors were naive, others thought we were stupid, mad, or irresponsible, and a few suggested darker motives including raising our impact factor by publishing a citable paper. There were calls for a retraction, and one for an internal inquiry. Here are a few typical comments. "It is saddening that a prestigious publication such as *BMJ* has lowered its publication standards to the point of letting a piece of rubbish occupy its columns and amplifying it with a complaisant editorial." "I cannot believe that a reputable journal such as the *British Medical Journal* can seriously print such a flawed study except to increase readership and create controversy" and "*BMJ*, what have you done?" The outrage had three themes: the study was bad for public health and should not have been published. Its conclusions were unreliable because the tobacco industry paid for them. And the methods and analysis were scientifically flawed. How could the paper have got through peer review? You can read our reviewers' comments, and an original, unedited draft of Davey Smith's editorial on bmj.com.

A dozen or so readers defended us. "You are to be congratulated for having the courage to publish research that, while politically incorrect and therefore destined to be excoriated by the anti-smoker lobbyists (many of whom work for anti-smoking organizations and therefore have obvious conflicts of interest even if they refuse to cite them) meets these criteria. Take solace that you are only being bashed verbally—Galileo paid a greater price for promulgation of his research that challenged the worldview of the catholic majority," wrote the director of facilities at an American university. She had no competing interests to declare.

Neither did most other respondents, despite some giving tell tale addresses such as Smoke Free Educational Services Inc, Smoke Free Pennsylvania, Adults Saving Kids, and Forces International (an advocacy group for smokers). One reader thought the *BMJ* was being ironic, asking them for a competing interest statement, and a few others simply wrote "I enjoy smoking" or "I quit smoking." Enstrom and Kabat wrote over 200 words explaining their funding and competing interests, but it wasn't enough. Both were accused of "swimming with sharks" and asked to clarify their dealings with the tobacco industry. One of them, Geoffrey Kabat, did so, adding, "To imply that skepticism about the 'weak association' of passive smoking with heart disease and lung cancer is due to influence from the tobacco industry is simply wrong-headed. There is legitimate debate about the effects of passive smoking on heart disease and lung cancer. The evidence is not as uniform or as strong as the activists and scientists with extra-scientific agendas make out." James Enstrom has clarified his dealings with the tobacco industry in BMJ/2003/084269. Richard Horton, the editor of the *Lancet*, concluded that the entire medical community is guilty of muddled thinking on conflicting interests.

Many letters were highly charged and hostile. "It is astounding how much of the criticism springs from Ad Hominem argument rather than from scientific criticism of the study itself," wrote a "private citizen" from Philadelphia PA. "As a publisher of the leading Austrian medical online news service I feel quite embarrassed following the debate on this article. Many postings look more like a witch hunt than a scientific debate," wrote another. It got bitter, and at times personal. A great read for anyone who enjoys a scrap. Disappointing for readers looking for a dispassionate appraisal of Enstrom and Kabat's study and its implications.

Alison Tonks *associate editor*
BMJ

1 Enstrom J, Kabat G. Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98. *BMJ* 2003;326:1057-61. (17 May.)
2 Davey Smith G. Effect of passive smoking on health. *BMJ* 2003;326:1048-9. (17 May.)

Comment from the editor

EDITOR—I can't respond to all the points raised in this debate, and I thought I would simply share some reflections.

Firstly, we've considered again whether we should we have a blanket policy of refusing to publish research funded by the tobacco industry. We've twice considered this question in the *BMJ* and twice decided against. The *BMJ* is passionately antitobacco, but we are also passionately prodebate and proscience. A ban would be antiscience.

Secondly, we are not in the "truth" business. Scientific truths are all provisional. Most of science falls away as new paradigms emerge. This doesn't mean that we are in the "lies" business, but we are in the "debate" business. We judged this paper[1] to be a useful contribution to an important debate. We may be wrong, as we are with many papers. That's science.

Thirdly, with research papers we first ask if we are interested in the question. We must be interested in whether passive smoking kills, and the question has not been definitively answered. It's a hard question, and our methods are inadequate.

We then peer review the study, but we are well aware of the extreme deficiencies of peer review. Of course the study we published has flaws—all papers do—but it also has considerable strengths: long follow up, large sample size, and more complete follow up than many such studies. It's too easy to dismiss studies like this as "fatally flawed," with the implication that the study means nothing.

Fourthly, I found it disturbing that so many people and organisations referred to the flaws in the study without specifying what they were. Indeed, this debate was much more remarkable for its passion than its precision.

Richard Smith *editor*
BMJ

Competing interests: RS is the editor of the *BMJ* and accountable for all that it publishes.

1 Enstrom JE, Kabat, GC. Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98. *BMJ* 2003;326:1057. (17 May.)

January 9, 2003

To: Editor Roger Robinson

From: James E. Enstrom

Geoffrey C. Kabat

RE: Response to BMJ/2002/011163 Manuscript Decision

Our response is given below in bold italics throughout the very helpful comments received from the editorial committee, two reviewers, and Professor Evans. We have done extensive new analyses in order to fully address the exposure misclassification issue and other major points and have presented our results in revised text and tables. Our revised paper is submitted along with this response. Because of the word limitation imposed on the text of the paper, many of the details in our response are not in the paper.

Date: Fri, 15 Nov 2002 07:59:20 -0800 (PST)

Subject: BMJ -- Manuscript Decision

Dear James E Enstrom:

MS ID#: BMJ/2002/011163

MS TITLE: ENVIRONMENTAL TOBACCO SMOKE AND CORONARY HEART DISEASE MORTALITY IN THE AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY, 1960-98

Report from the BMJ's editorial advisory committee meeting - 11th November 2002. Members of the committee were:

o Roger Robinson (Chair and note taker) o Nick Freemantle o Christopher Martyn o Stephen Evans

The editorial committee makes the final decisions on accepting original papers submitted to the journal. A little over 10% of papers reach this stage, and to do so they have passed a preliminary screening by one or more of the editors, and have received a reasonably positive external review. These comments are an attempt to summarise the discussions of the editorial committee. They are not an exact transcript. Referees reports are always fully taken into account by the committee, but the final decision on acceptance or rejection of a paper rests with the editorial committee, who take into account not only the scientific merits of the paper but also its originality and interest to a general readership in comparison with other submitted papers. We are only able to accept a small proportion even of the good papers submitted to us.

Decision: Reject but offer to review a substantially revised and shortened paper

Nature of decision: Majority

1. We recognised that this is a large and important data set, and also that this is a controversial and political area, with the BMJ having a general policy in favour of reducing smoke exposure. We therefore think it important that we should be prepared to present contrary findings provided everything has been done to ensure their validity. However, we do have concerns on that point, some of which are listed below and some are dealt with in the epidemiological and statistical reviewers' reports. We will only be happy to accept a revision if all these points are satisfactorily dealt with.

We have provided a point-by-point response below.

2. The paper at present is very long, and it needs to be reduced to not more than 2,500 words, with as many tables as are necessary. For reasons explained below, the meta-analysis should be omitted, and this will allow for substantial shortening.

The paper now has 2,500 words and 10 tables. Additional material can be put in the electronic version. The meta-analysis has been omitted, although comments about it are included in our responses below.

3. The data you are presenting are those from the California Subset of CPS. In places we were confused as to whether it was this or the whole of CPS I that was being discussed and even more confused on the penultimate page when you mention CPS II. We think you should essentially stick with California CPS.

We have limited the text to California (CA) CPS I, except for brief reference to previous ETS findings from the whole CPS I (references 10, 11, 16). No reference is made to CPS II.

4. We do not want the meta-analysis. It does not include all the mention we would normally want in a meta-analysis, for example on tests for quality of studies and publication bias, as well as all the data in the form of 2x2 tables for each study. You can include one paragraph in the discussion about how this study compares with other studies, and to what extent the confidence intervals in this study overlap with those of previous studies.

We have omitted the meta-analysis but have included a few sentences comparing our findings with those of other ETS studies and estimating the impact of our CHD findings on a new meta-analysis. However, we hope that we might be able to discuss with you at a future time why our meta-analysis represents an important contrast to the 1997 BMJ meta-analyses (references 4 & 8).

5. Our understanding is that the weakness of CPS I from the point of view of answering this question was the possibility of misclassification, on the basis of just using baseline smoking status in 1960. The strength of this study is that you have information on current status in CPS - CA on the basis of the 1999 questionnaire. But we think that you must acknowledge more fully that this questionnaire had a low response rate, and furthermore, that it did show evidence of misclassification. You should also acknowledge that misclassification will tend to bias the findings towards the null.

In the Methods and Results we now clearly acknowledge the low response rate of the 1999 questionnaire, its evidence of misclassification, and the fact that nondifferential misclassification will tend to bias the findings towards the null.

6. We do think there is a great potential for measurement error, and therefore misclassification over ETS exposure, possible misclassification of causes of death, and loss to follow-up.

We have dealt with the issues of misclassification of ETS exposure and causes of death and loss to follow-up in a number of ways. We have revised the presentation of our results (see new Tables 4-9) to make maximum use of smoking data from 1959, 1965, 1972, and 1999. We have added new results for subjects aged 50+ years at entry (born before 1910) and for subjects redefined as of 1972 and 1999—both of these subgroups

have less ETS exposure misclassification, particularly the females. See Tables 4-6 for exposure data and Tables 7 & 8 for RRs. Also, we have presented RRs for the short follow-up periods of 1960-65, 1966-72, and 1973-85 using the 1959, 1965, and 1972 definitions of smoking status (Table 9). Misclassification would presumably be less than that shown in Tables 4-6 during these short periods. During 1960-65 follow-up was 99% complete and ACS obtained death certificates for almost all deaths (see Table 1). Also, we have shown in Tables 2 & 3 that the proportion of subjects withdrawn/lost to follow-up through 1998 or with unknown cause of death was not related to their spousal smoking status. The short-term RRs are no different than the long-term RRs. Other ETS cohort studies have not presented these kinds of misclassification and follow-up details, and yet these errors exist in the other studies.

7. The strengths of this study are its size and the length of follow-up. But these advantages may be partly illusory. The quality of the data is more important than the size of the study, and a very long follow up may tend to bias results towards the null.

We have discussed the quality of the data in terms of follow-up status (Table 1), spousal smoking status (Tables 2 & 3), and misclassification (Tables 4-6). RR results for 26- & 39-year follow-up periods are in Tables 7 & 8, and RR results for 6-, 7-, & 13-year follow-up periods are in Table 9. All RR results are null. While it is possible that a very long follow-up may tend to bias results toward the null, no positive ETS relationships were found during the short follow-up periods. A very strong positive relationship with active cigarette smoking was found during the full 39-year period (Table 10), showing that true relationships can be detected with great precision in this cohort.

8. Professor Evans' statistical report raises some detailed questions about the numbers in the tables, particularly tables 2 and 3 and these issues are raised in his report.

The numbers in the tables are clarified in our new tables and in our response to his statistical report.

In order that there should be no misunderstanding, I must make it clear that the present status of the paper is that it is rejected, but that we are prepared to review a revision, but with no promise about final acceptance. The following points are the ones that we always make to authors from whom we are inviting revisions, and you will need to take all these into account if you do decide to resubmit.

We hope that our revised paper and responses are satisfactory, but if not we hope you give us a final chance to resolve any remaining issues because we believe that we have been able to successfully address most of the concerns that you have and to greatly strengthen the paper in the process.

Original papers in the BMJ are now published in two forms - a full version on our website and a shorter version in the printed journal. For a full explanation of our ELPS (electronic long, paper short) system see the Editorial by Mullner and Groves in our issue of 31 August 2002 (Vol 325, p. 456), which you can access at http://www.bmj.com/cgi/reprint/325/7362/456.pdf. As you will see, we only need from you the revised version of the full paper, and the main text of this should not exceed the word count given below. We will produce the shorter version.

When you revise and return your manuscript, please take note of all the following points. The commonest reason for us to have to bounce papers back to authors after revision is that some of these points have not been attended to. The paper will not be accepted until they all have. Even if the item was correct in the original draft, you need to check that it has not slipped out in the revision:

a. In your covering letter indicate point by point your replies to the points made by the referee and the editorial committee and how you have dealt with them in the paper. Within the word limit it will probably not be possible to deal in any detail with all these points in the paper itself but we would like your answers in the covering letter.

Instead of a covering letter, we have provided a detailed reply in bold immediately following each point made by the editors and reviewers.

b. Do not exceed 2500 words of text. Please include a word count on the title page.

The word count is now 2,500.

c. The title should include the study design

The new title includes the "prospective study" design.

d. Please include a paragraph for "This week in the BMJ".

The proposed paragraph is:

> **Exposure to environmental tobacco smoke was not associated with mortality from tobacco-related disease in a large prospective study.**
>
> **Active smoking is an established risk factor for coronary heart disease, lung cancer, and chronic obstructive lung disease. Whether exposure to environmental tobacco smoke is associated with increased mortality from tobacco-related diseases is less clear, due to the difficulty of accurately assessing exposure and other methodological problems. Mortality from coronary heart disease, lung cancer, and chronic obstructive lung disease was investigated by Enstrom & Kabat (p) in a large cohort of Californians with nearly forty years of follow-up. No association of exposure to spousal smoking was found for any of the three outcomes in either males or females. In contrast, active smoking showed a clear dose-related association with mortality from all three tobacco-related diseases. Efforts to reduce active smoking are likely to have the greatest impact on tobacco-related mortality.**

e. Please include a box saying "what is already known on this topic" and "what this paper adds".

What is already known on this topic

- ***Active smoking is an established risk factor for tobacco-related mortality.***
- ***Whether exposure to environmental tobacco smoke (ETS) is associated with increased mortality from tobacco-related diseases is less clear, due to the difficulty of accurately assessing exposure and other methodological problems.***

What this paper adds

- ***We investigated tobacco-related disease mortality as a function of spousal smoking in a large cohort study with forty years of follow-up and periodic updating of exposure information.***
- ***No association of exposure to spousal smoking was found with mortality from coronary heart disease, lung cancer, or chronic obstructive lung disease.***
- ***The findings from this large study suggest that the effects of ETS exposure may be smaller than generally believed. This is consistent with the greater dilution of ETS compared to directly inhaled smoke.***
- ***Efforts to reduce active smoking are likely to have the greatest impact on tobacco-related mortality.***

f. Please include the names and positions of the authors on the title page. Make sure that the name and contact details of the corresponding author are clearly shown on the title page. Include the email address if there is one.

The author information and contact details are on the title page.

g. Please supply signatures of all the authors, and signed competing interests forms for each author, if you have not already done this.

Signed competing interest forms have been faxed to BMJ.

h. Please include a contributorship statement at the end of the paper, with the name of the guarantor. We require contributors to disclose details of their own and their funders' roles in the study.

The contributorship statement for the authors has been included at the end of the paper. None of the funders has had any control over the extended follow-up or analysis of the study. None of the funders have seen this manuscript or had any role in its preparation.

i. The guarantor must provide us with a signed statement that he/she accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish (see editorial by Richard Smith, BMJ 2001;323:588).

James E. Enstrom is the guarantor and he accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish. This statement has been included on the competing interest form, which has his signature.

j. Please include a statement about ethical approval and about funding.

ACS initiated the study in 1959 and conducted follow-up through 1972. Extended follow-up through 1998 has been conducted at the UCLA School of Public Health with funding from the University of California Tobacco-Related Disease Research Program and the Center for Indoor Air Research. This statement about funding has been included at the end of the paper. The UCLA IRB has approved this research study involving human subjects during the time research has been conducted at UCLA.

k. Do not exceed 24 references

There are now 21 references.

l. We would like your revision back with us within two months of your receiving this report: earlier is better!

We have replied within the requested time period.

Yours sincerely, Professor Roger Robinson FRCP

Reviewer 1 Comments for the Author

Name: Kenneth J. Rothman

Position: Senior Scientist

This is a potentially important study that presents relevant data on a topic of broad interest. These data should be published. Before publication, however, the presentation could use improvement in a couple of areas.

The major concern is insufficient attention in the manuscript to a potentially important source of bias, nondifferential misclassification. In previous studies, which found a relation between ETS and CHD mortality, there was less need to be concerned about bias from nondifferential misclassification than in this study, because nondifferential misclassification can explain a null effect but will not falsely produce a positive finding. But here the finding is essentially null. As a result, the authors ought to be preoccupied with the extent to which nondifferential misclassification exists in their study population, and the extent to which it has biased their findings.

While the reviewer has raised an important issue, he apparently does not realize that very few of the previous studies actually found a significant positive relation between ETS and CHD mortality. While many previous studies have found RRs above 1.0, most RRs were NOT significantly different from 1.0 and thus constitute NO relationship. See the ETS-CHD meta-analysis table of US cohort studies at the end of our response (taken from the original version of our paper). It was only when these largely insignificant results were combined in a meta-analysis that a significant summary RR resulted. The other cohort studies have not addressed the impact of smoking misclassification or exposure misclassification on their results.

Certainly some nondifferential misclassification exists in this study. Smoking in a spouse is not the only source of environmental tobacco smoke. The most important additional source would likely be workplace exposure (which is documented in the data presented in table 4), but there are also other sources of exposure that those with nonsmoking spouses will have experienced. Also, some people with a smoking spouse may get little exposure, depending on the when and how the spouse smokes. The net result will be nondifferential misclassification and bias toward the null. What can be done about it? One thing is to focus on this problem in the discussion section. Another is to present a sensitivity analysis that shows the extent to which nondifferential misclassification may have biased the study results.

In response the reviewer's comments, we have included additional data and discussion regarding exposure misclassification. We have now determined that exposure misclassification is substantially reduced in certain subgroups, such as, subjects aged 50+ years at entry (Table 4), subjects defined as of 1972 (data not shown), and subjects defined as of 1999 (Table 5). Also, misclassification is relatively small in the key reference group, never smokers whose spouse never smoked. In spite of its limitations, our data clearly show that spousal smoking is related to total self-reported ETS exposure, particularly for women.

We demonstrate with an example similar to one in Rothman & Greenland, MODERN EPIDEMIOLOGY, p.128 that the effect of nondifferential exposure misclassification is not enough to obscure a true ETS-CHD relationship if it existed, particularly among women. Using data from Table 4, the effect of nondifferential misclassification on CHD RR is shown below for 1959 female never smokers aged 50+ years at entry, assuming current spousal smoking increases CHD risk by 30% (meta-analysis RR=1.30).

1959 spousal smoking	"Total ETS exposure" (no misclassification) None/ light	Moderate/ heavy	CHD RR (m-a)	"Total ETS exposure" (nondiff misclass from Table 4) None/ light	Moderate/ heavy	CHD RR (corrected)	Actual 1960-98 CHD RR (females aged 50+) (Table 8)
Never (n)	100%	0%	1.00	93.1%	6.9%	1.021 (=.931+1.3x.069)	
Current (c)	0%	100%	1.30	42.2%	57.8%	1.173 (=.422+1.3x.578)	
RR(c/n)			1.30			1.150 (=1.173/1.021)	0.98 (0.91-1.06)

RR(c/n)=1.30 with no misclassification is reduced to RR(c/n)=1.150 with the level of nondifferential misclassification shown in Table 4. However, RR(c/n)=1.150 is still greater than the measured RR=0.98 (0.91-1.06) for females aged 50+. A similar calculation for all females yields reduced RR(c/n)= 1.1557/1.045=1.106, which is still greater than the measured RR=1.01 (0.93-1.09). Misclassification is a more serious problem among males and could obscure weak relationships and we acknowledge this. However, this situation is true for the other ETS-CHD studies as well. Keep in mind that Table 4 shows misclassification from 1959 to 1999 and exposure misclassification was less over shorter periods of time based on Table 5 and other evidence.

Although not mentioned by the reviewer, we have examined smoking misclassification bias in Table 6 using 1965, 1972, and 1999 smoking data. Smoking misclassification is a bias away from the null but is not a serious concern in our cohort because the level of misclassification is small and the RRs are close to 1.0.

Other changes that should be considered: 1) This is a cohort study, which has the theoretical advantage that it can provide actual rate information, as opposed to case-control studies, which provide only relative risks. Nevertheless, the authors report only relative risk. They should be encouraged to present actual rates for their cohort, giving the number of deaths and the person-year denominators for all of the rates that they present. They should also give a breakdown of the rates, with numerators and denominators, stratified by age and sex and perhaps other variables as well as exposure. 2) The authors focus much too heavily on significance testing. I consider this to be a mistake in itself, but even more so here when the issue is not so much the compatibility between their findings and a null effect as it is between their findings and the previously reported non-null results. They should discard their significance testing focus and instead emphasize only the magnitude of their effect estimates and their confidence intervals.

1) The total number of deaths and subjects are included for each RR in Tables 7-9 and can be used to calculate the actual (crude) death rate. Also, the 1960-98 age-adjusted death rate (DR) for all never smokers for each cause has been presented Tables 7 and 8. The approximate age-adjusted DR by spousal smoking status can be obtained by scaling the overall age-adjusted DR with RR. There are a number of complications that make it very difficult to present age-adjusted DRs instead of RRs: few deaths in some age groups and/or categories result in unstable age-adjusted DRs; the changing age distribution of subjects over 39 years of FU means all deaths & person-years in later FU years are added to older age groups; difficulties in adjusting for confounders; difficulties in calculating confidence intervals. Keep in mind that essentially all other ETS cohort studies have presented RRs and not DRs, and we should not be held to a completely different standard. However, additional age-adjusted DRs can be provided in a final version of an accepted paper where considered particularly valuable.

2) We do not understand why the reviewer thinks we focus too much on significance testing. In fact, most of our results are presented in the form of RR (95% CI) and we do not present any P-value statistical tests. The reviewer continues to mistakenly assume that most of the previously reported results are non-null, when in fact they are largely consistent with our null results (see the meta-analysis table).

Reviewer 2 Comments for the Author

Environmental tobacco smoke and coronary heart disease mortality in the American Cancer Society cancer prevention study, 1960-98

This is an important contribution to the literature an environmental tobacco smoke and coronary heart disease mortality. It is not currently in a format suitable for the BMJ, having 10 tables and an appendix, but all the information included (and more; see below) should be made available, by combined paper and web publication. In this controversial area the easier it is for results to be checked and verified the better (as illustrated by the previous analysis of the same cohort, their reference 8, which was published as a section of a highly partisan paper on the issue and has been discredited because of this).

The present study presents data from follow-up over nearly 40 years of one section of the American Cancer Society Cancer Prevention Study I (CPS I), representing about 10% of the overall CPS I cohort from which the controversial analyses referred to above, for a shorter follow-up period, are available. Of formally reported studies, the present one has about as much power as the largest previous study, from the American Cancer Society Cancer Prevention Study II (their reference 23) and certainly adds substantially to the overview of all findings.

Several major issues with presentation and analysis need to be dealt with, however.

The first - a crucial issue in this field - is that exposure measurement for environmental tobacco smoke is poor, leading to substantial under-estimations of the strength of any associations. The important exposure is the amount of ETS breathed into someone's lungs over many years. Proxy measures of this exposure are used - reported global ETS exposure, or more commonly spousal smoking, which would relate to the amount of ETS breathed in, although obviously it would be an imprecise measure of this. Because of the major effect of personal cigarette smoking on risk of coronary heart disease, which would be impossible to adjust for in any analysis, the appropriate analyses - as carried out here - are on never smokers with smoking spouses. Data on misclassification are, appropriately, fully presented in this paper. What is seen is that there is misclassification of own smoking status, with around 7% of the apparent never smokers in 1959 reporting that they were former smokers in 1999, (among the relatively small number who were followed up in 1999). This could confound any association between spousal smoking and outcome. Secondly, when using 1959 spousal smoking status over 10% of people whose spouse smoked in 1959 reported (in 1999) that they never lived with any smoker. Nearly a quarter said that they had never had regular exposure to cigarette smoke from others in work or daily life. Thus even misclassification of spousal smoking status seems to be substantial, and when it is taken into account that spousal smoking status is only a proxy marker for the amount of ETS breathed into the lungs, it is clear that there is a considerable amount of potential misclassification. The statement in the methods section, that this misclassification will only lead to bias by a small amount, is potentially misleading and should be qualified. If misclassification is differential then the degree we are talking about here could have a substantial effect. Only if the misclassification is non-differential and the overall relative risk is very close to 1 can what is stated here be accurate.

The present study has substantial data, given the very high proportion of participants who are now dead. It is clear from comparing the event proportion in the follow-up to 1972 with the event proportion in the present follow-up that the large majority of deaths occurred since 1972. Therefore an analysis could (and should) be performed on participants who survived to 1972 and were followed up in 1972, for whom it is possible to improve classification of never smoking status (the not inconsiderable proportion who either reported they were former smokers or current smokers in 1972 would be excluded). More importantly, those whose spouses had remained with them and reported being smokers in 1959, 1965 and 1972, would give much better classification of time density and continuity of exposure. For this group spousal smoking should be related to coronary heart disease mortality post-1972. The data are clearly available to the investigators to carry out this simple analysis.

The reviewer has made a very good suggestion. We have determined that the degree of exposure misclassification between 1972 and 1999 is less than the misclassification from 1959 to 1999. A full analysis of 1973-98 RRs has been added, as well as new analyses for even shorter periods of 1960-65, 1966-72, and 1973-85. The 1965 and 1972 questionnaires asked about current smoking but not former smoking and thus have been used to remove current smokers but not former smokers. Only the 1959 and 1999 questionnaires collected full smoking histories. Additional analysis (see new Table 6) shows that the majority of 1959 never smokers with a 1999 smoking history had smoked 10 or fewer cigarettes per day for only few years and had quit before 1960. Active smoking misclassification among never smokers was not as serious as it appeared before analyzing level and years of smoking.

The addition of the updated meta-analysis to the present paper is a valuable and necessary one. However no case can be made for excluding the non-US studies (apparently 2 cohort studies). There is no *a priori* reason to believe that ETS should have a different biological effect in the US and in what are, unfortunately, referred to as "foreign" countries in the present paper. Indeed it is more likely that a distinction is drawn because some differences in findings have been seen in previous meta-analyses. The meta-analyses that have been carried out should report the heterogeneity statistics, and should also perform statistical tests for publication bias, given that publication bias has been considered to be an important issue in the ETS field.

Currently the authors have performed a meta-analysis including their analyses and also those on the full CPS I cohort, which includes their study as a subsample. This is clearly inappropriate double counting. This could be avoided by producing just the results for deaths from 1972 to 1998 in their subgroup, and adding this to the overall meta-analysis, or, as clearly the whole CPS I data with follow-up to 1972 are available to the authors, performing analyses on the full cohort up to 1972 excluding the California group.

While we agree with the reviewer that the meta-analysis is valuable, we have removed it at the request of the editors and the above points have not been addressed. As a point of clarification, we only have access to the California subjects in CPS I, not the entire CPS I cohort.

There is considerable literature - and controversy - regarding the potential association between ETS and lung cancer and chronic obstructive pulmonary disease mortality. This too is bedeviled by publication bias and a report from a large study such as the present one which does not give outcome data for consideration for these other outcomes would be unfortunate. With lung cancer and COPD exclusion of all personal smokers from the cohort is key, so reports for the well characterized subgroup using mortality data post-1972, as suggested above for CHD, would be valuable, together with the overall effects on lung cancer and COPD. Being able to see all the results together would help with their mutual interpretation. For example, if an effect was seen on COPD or lung cancer, it would strongly support the notion that there were considerable differences in ETS exposure between the groups, and therefore that ETS exposure genuinely has no effect on coronary heart disease (rather than the null result reflecting poor measurement of ETS exposure).

The reviewer has made another excellent suggestion. Results for lung cancer and COPD have been added to Tables 7 and 8. Our 1960-98 lung cancer RRs are consistent with the 1960-72 lung cancer RRs published for the full CPS I (reference 16). Our paper presents the first detailed mortality results on ETS and COPD. There are several RRs for COPD that are above 1.0, but the 95% CI includes 1.0 for all RRs.

Specific points

The suggestion that the results are not likely to be affected by misclassification of ETS exposure or smoking status should be removed from the abstract. Similarly the concluding statement that the strong relationship between cigarette smoking and CHD deaths appears to be more persistent than generally believed amongst personal smokers should be removed from the conclusions of the abstract and from the discussion. The analysis reported here is not the appropriate one to examine this issue (the appropriate analysis would be a formal analysis of the time course of the decline of CHD risk among ex-smokers, given time from quitting) not just the analysis of mortality amongst smokers over time with the vague statement that many of them had given up, and no attempts to model what this should mean for the relative risks. It has been convincingly argued that smoking has a cumulative effect on disease risk, and that people who have smoked for 40 years have increased risk compared to those who smoked for 20 years. Thus a stable overall risk relationship with baseline smoking over time could reflect two tendencies in opposite directions - a tendency for the association to go down because some people quit smoking - and a tendency for the association to get greater because the continuing smokers accumulate more continuous years of smoking.

The objectionable statements have been removed as requested. The active smoking results are now limited (new Table 10), primarily to demonstrate that we can precisely measure the strong relationship between active smoking and tobacco-related mortality in this cohort. Also, Table 10 indicates smoking one cigarette per day can increase CHD risk by only a small amount (RR~1.05), far less than the large amount (RR~1.39) claimed in reference 4.

In the methods section when the 1999 survey is described the fact that only 14 male and 31 female questionnaires were completed by the wrong person does not confirm that addresses had accurately located subjects, because presumably the questionnaires were addressed to someone and the fact that rather few people

of different names filled in questionnaires merely shows that people read what is on the envelope or the questionnaire.

The persons who responded to the 1999 questionnaire were asked in the cover letter if they recalled CPS I and were properly located. Each respondent had to confirm their full name and enter unique identifying information such as date and place of birth, height, weight, education, and occupation. All their 1999 responses were checked against their original 1959 data. More than 99% of respondents provided 1999 identifying data that was consistent with the corresponding 1959 data, thereby indicating they were indeed CPS I subjects; the invalid 1999 responses from 14 males and 31 females were discarded.

The term "race" is used in table 1. Is this what the authors mean, or were the data that were collected self-identified ethnicity?

The data in Tables 2 and 3 were self-identified race. Essentially all CPS I subjects are of the white race.

In table 8 the second row of results should be for 1973-1998 follow-up not the 1960-1998 follow-up which also includes the mortality presented in the first row. It would be much easier to see what is going on over time if independent analyses were presented.

Table 10 (formerly Table 8) has been greatly simplified to show only 1960-98 active smoking results and there is no longer any discussion of trends.

To the editor

This paper makes an important contribution to the literature on ETS and coronary heart disease, and should certainly be published. There are a large number of issues regarding analysis and presentation that need to be dealt with before it is acceptable, however.

Statistical Report on BMJ 011163 ETS and CHD

This paper is a complex report on a complex cohort study with very long term (38 years) follow-up. It finds essentially no association between environmental tobacco smoke (ETS) and coronary heart disease (CHD) mortality. This report is written by a statistician who has seen the other reviewers' reports and will not go into their comments again in any detail. The main findings are that the estimated relative risk was an overall 0.99 with 95% CI 0.93 to 1.06. They also found a strong relationship between active smoking and CHD mortality that persisted over the entire time period.

The authors claim, in the Abstract, that "The results are not likely to be affected by misclassification of ETS exposure, since these errors appeared to be small". This assumes that other studies have not been affected by misclassification since they found an association, and that this study would find an association in spite of misclassification if such an association truly exists. The problem is that this study should be examined on its own merits, and the idea that exposure misclassification is negligible seems to be naive at best.

There are a number of factors that will bias the observed association towards a null value (assuming a real association does exist). 1) ETS exposure itself; 2) loss to follow-up (spouses of non-smokers who are smokers will have reduced life-expectancy compared with spouses of non-smokers who are also non-smokers) – this may mean that follow-up of those exposed to ETS is more likely to be lost because of moving, remarriage etc 3) misclassification of cause of death 4) in any proportional hazards model with very long FU, survival curves will tend to approach one another.

While errors increase with long follow-up they are not unusually large at any time and they are minimal for the short follow-up periods of 1960-65 and 1966-72. For instance, the loss to follow-up was only 1% as of 1965 and 1960-65 RR results are no different than later results. Tables 2 & 3 show that the proportion of those lost to follow-up and the proportion with unknown cause of death vary only slightly by spousal smoking status. There is no evidence of misclassification of cause of death by spousal smoking status or otherwise. For instance, we have confirmed that for the underlying cause of 1960-72 deaths there was good agreement between the death certificates obtained by ACS and the California death file used by us, where State Nosologist assigns ICD code. While point 4 is true to some extent, note that the short-term RRs in Table 9 are consistent with the long-term RRs in Tables 7 & 8. Also, point 4 does not have a major impact on the strong active smoking RRs in Table 10.

The referees have discussed some of the issues of ETS exposure misclassification. In the early years of this study, it seems likely that ETS exposure for non-smokers may well have been related as much to exposure in the workplace as at home. The amount of ETS exposure may relate to a variety of factors in addition to crude estimates of spousal smoking. The authors claim that spousal smoking in 1959 is relatively constant, and use Table 4 as a key component of their argument. My interpretation of this table is somewhat different. Perhaps I have misunderstood. Of those non-smoker males whose spouse was said to be a non-smoker in 1959, 42% had no regular exposure to cigarette smoke, but equally 58% did have regular exposure. Nearly 5% lived with a smoking spouse. At the same time among those with smoking spouses, at least 20% stated they had no regular exposure to cigarette smoke. A similar pattern exists among female never smokers but as might be expected, those whose spouse was a never smoker in 1959, 61% did not have regular exposure to cigarette smoke, but 39% did have such exposure. This to me is very considerable misclassification of exposure to ETS. The uncertainty in these data is very high since those still left to have exposure to ETS assessed in 1999 are a small and biased sample of those in the whole study.

We think the reviewer is making too much of our misclassification data, which was based on self-described qualitative ETS exposure history over a lifetime. We were simply trying to confirm in a crude way that spousal smoking was related to ETS exposure, something that has not been done at all in the other ETS cohort studies. However, to further examine this issue, we have now shown in the new Tables 4 & 5 that the misclassification errors were smaller for certain subgroups, such as, subjects aged 50+ years at entry and subjects classified as of 1972 and 1999. Also, because of death before 1999 the older CA CPS I subjects were very underrepresented in the 1999 survey: ~58% of 1959 subjects were aged 50+ at entry, but only ~16% of 1999 respondents were aged 50+ at entry. Although the multi-level ETS index based on spousal smoking was clearly related to total ETS exposure (Table 4), the RRs based on the ETS index showed no hint of any trend except for COPD.

The consequence of this is that the authors must provide some form of sensitivity analysis to allow for a variety of sources of misclassification. The assumption in this study is that the only errors are sampling errors related to the size of the study, importantly related to the number of "events" (deaths in this case). This study has small values of sampling error, but it is entirely possible that its misclassification errors are much greater than other smaller studies. Greenland has suggested an elegant mechanism for carrying out sensitivity analysis for unmeasured confounding. The authors should either carry out a similar exercise for misclassification error or make some very strong statements warning of the possible errors that could explain their results. Their current strong statements, one of which is quoted above, are simply not justified.

A sensitivity analysis has been carried out above for Reviewer 1. Keep in mind that the other ETS cohort studies have not addressed the misclassification issue to any extent and misclassification errors surely impact their results. We have revised several statements regarding misclassification errors.

Other detailed points

1 Table 1 has an odd pattern for the FU. The ratio of F:M subjects gradually increases over time as might be expected from 1.3 in 1959 to 1.45 alive in 1972 to 2.2 in 1998. Among the never smokers with a spouse with known smoking, it was 2.7 in 1960 and 4.36 in 1998. The explanation for these big differences is not immediately obvious.

The new Table 1 provides more information. The F: M ratio changes above occurred largely because the female never smokers with spouses were younger than all females and thus had greater survival. This pattern has no impact on the resulting RR calculations.

2 In Table 2 the follow-up in 1999 is 6.7% for non-smoking males is 6.7% for never-smoking spouses, but 9.4% for those with Former smoking spouses and over 8% for those with current smoking spouses. Again the explanation for this is not clear.

It is not clear what percentages are being cited. In any case, the percentage of those lost to follow-up is not large and does not differ significantly by spousal smoking status.

3 In Table 2, those with a never-smoking spouse had notably lower education levels than the smokers. In Table 3, this is reversed.

Although, there are some differences in education (% > 12 years) by spousal smoking status in Tables 2 & 3, the differences are not large when the full distribution of education levels is considered and used in the PHREG model.

4 Table 4 has the first column headed "1959 spousal smoking subjects". This may be a result of different formatting for US as opposed to International-sized paper, but it is confusing as it stands.

This is simply a formatting problem. The first column heading should read "1959 spousal smoking". The word "subjects" belongs over the last column.

5 Table 8 has some strange patterns. For example among females there were 818 in the 1960-72 FU who smoked 40-80 cigarettes/day. There were 15 deaths. This leaves 803 potentially available for FU 1973-98. This is the number seen at the bottom of the table. For the males however, the corresponding numbers are 2621 with 222 deaths leaving 2399 available for FU but only 1051 are listed in the last row of the table.

The strange patterns are due to different smoking definitions in 1959 and 1972. The 1960-72 and 1973-98 data are now omitted from Table 10 (formerly Table 8), which is now limited to 1960-98 data.

6 The total number of deaths seems inconsistent in Table 8. There are 222 deaths 60-72 and 208 deaths 73-98 among males, but 573 deaths between 1960-98. This means that there are 143 deaths missing in the separate sections of the FU. Now this could be because the smoking categories in the 1973-98 section are based on smoking in the 1972 data, but there ought to be a line that gives those for whom data in 1972 are missing. For the females the opposite is true; there are 15 & 103 deaths in the separate sections but 111 in the total period- 7 deaths extra occur in the separate periods. It is possible that this is just co-incidence since the numbers in the different categories in the 1972 smoking status may be very different. In nearly all instances the totals for 1960-98 deaths are more than those for 60-72 and 73-98 combined. The consequence of this seems to me that there are a number of changes over time, and with a non-randomised study interpretation should be cautious. The authors may say that other authors who HAVE found an association were not cautious in their interpretation, and I would heartily agree with them! This does not mean that this paper should simply redress the balance by having too strong interpretations of their data.

The whole issue of active smoking has been greatly simplified in the text and Table 10. The revised paper does not attempt to discuss trends involving active smoking.

7 Methods, paragraph 3: It is not clear how the matching was done. Was a perfect match necessary? Was any form of probability matching used?

Death matching is explained in more detail in our earlier CA CPS I paper (reference 18). Briefly, matching was done by creating a matching score based on components of full name, date and place of birth, sex, race, spouse's initials, and place of residence. Deaths with a high matching score were accepted as clearly valid. Questionable matches with a moderate score were resolved by a manual examination of all available information, including any possible matches with the drivers license file indicating that the subject was still alive. For most deceased subjects there was only one clearly valid match during 1960-98. Death matches were rejected for low matching scores.

8 Results: end of para 1. "a large portion of the subjects have been married only once". Actual data should be given here. The current statement is vague.

The 1999 marital history data are presented in Table 4 and show that over 80% of 1999 respondents have been married only once. These respondents were all aged 70+ years as of 1999 and would be more likely to have had multiple marriages than persons dying during 1960-98. Marital history was not determined in 1959, but based on the 1999 data and the fact that most women had the same last name at death as they had at entry, the vast majority of subjects have been married only once.

9 In para 9 of the discussion (starting "Second, the summary RRs ..") it says that "individual RRs were inappropriately combined". This is not clear. Any such combining of exposure categories must tend to lead to under-estimation of RRs. Using both incidence and mortality may not be invalid. RRS for each may be expected to be similar though absolute rates may be quite different.

Although now removed from the paper, our ETS-CHD meta-analysis of US cohort studies (the former Table 10, which is now shown below) was valuable because it showed separate results for RR(current/never) and RR(ever/never). This separation of exposures is important for CHD results because the published meta-analysis summary of RR(exposed/not exposed)=1.22 for US studies is substantially greater than RR(current/never)=1.18 and RR(ever/never)=1.11, based on the same studies. This overestimation occurred primarily because only RR(current/never)~1.16 from the very large CPS II study was used and RR(ever/never)~1.06 was ignored. The addition of our CA CPS I results to the meta-analysis yields RR(current/never)=1.05 and RR(ever/never)=1.05. Our meta-analysis table shows that all female RRs and most male RRs are consistent with RR=1.05. To summarize, the earlier CHD RRs are consistent with our RRs, and our RRs substantially lower the summary RRs for CHD. While the negative CA CPS I results do not alter the lung cancer meta-analyses, they certainly suggest the relationship is weaker than generally believed. Further discussion of available evidence can be done with a comprehensive new meta-analysis.

10 This paper should give absolute rather than just relative risks.

This issue has been addressed in detail in response to Reviewer 1. We have provided essential information on absolute risks (DRs) in Tables 7-9, along with relative risks (RRs). Additional DRs can be provided if necessary.

I agree with other reviewers that the meta-analysis is not suitable for this paper. Again, it is possible that previous systematic reviews have not been carried with as great care as they should have been, but this paper is not the place to redress that.

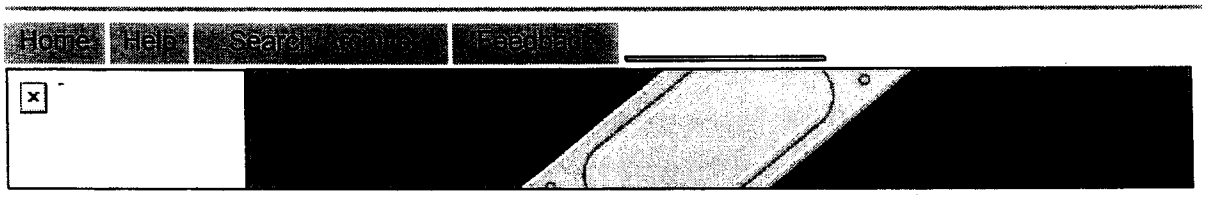
The meta-analysis has been removed from the paper.

SJW Evans

Meta-analysis Table. Meta-analysis of relationship between ETS exposure and CHD mortality for US cohort studies in Groups A, B, C. Relative risk (RR & 95% CI) compares never smokers with ETS exposure to never smokers with no ETS exposure. Signs used: ~ indicates RR was approximated from available published data; * indicates RR was based on combining other published RRs. Age-adjusted RRs were used, except for two studies (indicated by 'adj') that published only multivariate-adjusted RRs.

Study & Group	Relative risk by ETS exposure		
	RR (former/never)	RR (current/never)	RR (ever/never)
Males			
A Svendsen		2.11 (0.69-6.46)	
A Butler-AHSMOG			0.55* (0.31-0.99)
A Sandler-adj			1.31 (1.05-1.64)
A Steenland-adj	0.96 (0.83-1.11)	1.22 (1.07-1.40)	1.09* (0.99-1.21)
B Enstrom-CA CPS I	0.94 (0.78-1.12)	0.94 (0.83-1.07)	0.94 (0.85-1.05)
C LeVois-CPS I	0.95 (0.83-1.09)	0.98* (0.90-1.07)	0.97 (0.90-1.05)
Summary--A	0.96 (0.83-1.11)	1.23 (1.08-1.41)	1.11 (1.01-1.21)
Summary--A & B	0.95 (0.85-1.07)	1.07 (0.97-1.17)	1.03 (0.96-1.11)
Summary--A & C	0.95 (0.86-1.05)	1.05 (0.98-1.13)	1.02 (0.97-1.09)
Females			
A Garland	3.00 ~(0.8-12.0)	2.25 ~(0.5-11.0)	~2.73 ~(0.7-11.0)
A Butler-Sp Pairs	0.96 (0.55-1.66)	1.40 (0.51-3.84)	1.05* (0.64-1.70)
A Butler-AHSMOG			1.51* (0.99-2.29)
A Sandler-adj			1.19 (1.04-1.36)
A Humble		1.29 (0.79-2.10)	
A Steenland-adj	1.00 (0.88-1.13)	1.10 (0.96-1.27)	1.04* (0.95-1.15)

A Kawachi		1.87 (0.56-6.20)	
B Enstrom-CA CPS I	1.02 (0.93-1.11)	1.01 (0.93-1.09)	1.01 (0.94-1.08)
C LeVois-CPS I	0.99 (0.93-1.05)	1.04* (0.98-1.11)	1.03 (0.98-1.08)
Summary--A	1.01 (0.89-1.14)	1.13 (0.99-1.29)	1.11 (1.03-1.19)
Summary--A & B	1.02 (0.95-1.09)	1.04 (0.97-1.11)	1.05 (1.00-1.11)
Summary--A & C	0.99 (0.94-1.05)	1.05 (1.00-1.11)	1.05 (1.01-1.10)
Both Sexes			
Summary--A	0.99 (0.90-1.08)	1.18 (1.07-1.29)	1.11 (1.04-1.17)
Summary--A & B	1.00 (0.94-1.06)	1.05 (0.99-1.11)	1.05 (1.00-1.09)
Summary--A & C	0.98 (0.94-1.02)	1.05 (1.01-1.10)	1.04 (1.01-1.08)



March 5, 2003

To: *Editor Roger Robinson*

From: *James E. Enstrom*

Geoffrey C. Kabat

RE: *Response to BMJ/2003/039685 Manuscript Decision*

Thank you very much for provisionally accepting our paper. We have further revised our paper in response to the additional comments received from Professors Davey Smith and Evans. Our revisions are discussed below in bold italics throughout the comments.

In addition, we have recently found that widowhood was strongly associated with spousal smoking in the CA CPS I cohort, as we have now shown in revised Tables 2-4. Since smokers die sooner than nonsmokers, widowhood was increased among subjects married to smokers. Since widowed persons have higher death rates than married persons (references 22 and 23), the increased widowhood among subjects married to smokers would increase their death rate irrespective of exposure to ETS. Controlling for widowhood would be expected to decrease the RRs among those married to smokers. We have not recalculated the RRs in Tables 7-9 because they are already consistent with no effect and because we wanted to respond to you as soon as possible. However, we have added a few sentences to the text regarding widowhood because this confounder, which has not been considered in the other spousal smoking studies, might partially explain the positive RRs in those studies.

We hope that our latest revision is acceptable, but, if not, we are willing to continue to make additional refinements until it is as clear and accurate as possible.

Thank you very much for the generous consideration that you have given us on this difficult subject.

Date: Fri, 28 Feb 2003 03:56:20 -0800
Subject: BMJ -- Manuscript Decision

MS ID#: BMJ/2003/039685

MS TITLE: ENVIRONMENTAL TOBACCO SMOKE AND TOBACCO-RELATED MORTALITY

IN A PROSPECTIVE STUDY OF CALIFORNIANS, 1960-98

Dear James E Enstrom:

Paper 39685

We are impressed with the care you have taken over your revision, and we all agree that the paper is now getting close to acceptance. We would, however, like you to look at the further reports by Professor Stephen Evans and Professor Davey Smith. In Professor Evans's report we would like you to deal with the matters raised in his paragraphs 4, 6 and 7. The paragraphs are not numbered in his report but paragraph 4 is the one referring to the first phrase of the conclusions, paragraph 6 to the question of author bias" and paragraph 7 to the reservations about conclusions from studies of this kind.

From Professor Davey Smith's report we would like you to deal with the question of COPD and whether you should be more cautious in what you say about this.

I am sorry we have been some time over coming back to you with this response. We are very anxious to get this important and controversial paper as correct as we can before publication, and I am sure you agree with this. We are now very nearly there, and I hope you will be able to deal with these small points rather more quickly than we have dealt with your revision.

Yours sincerely

Roger Robinson

Reviewer 1 Comments ...

Name: George Davey Smith

I think the authors have done a good job dealing with the comments, and it should now go ahead for publication. I think my original comment regarding the updated meta-analysis still stands, but your editorial committee overrode this. My one disagreement with the current presentation of the paper is that the authors present it as totally negative, but if you look at the best estimate of the

association with chronic obstructive pulmonary disease, which is from the analysis I suggested of subjects defined in 1972 and followed-up 1973-1998, with the lowest level of misclassification of exposure through using repeat pre–1973 measures, for men there is a relative risk of 1.80 (0.78-4.17) and for women of 1.57 (0.84-2.96). I do not think these are negative findings – they are based on a small number of cases and therefore imprecise and the confidence intervals for the

sex-specific analyses include one, but the best estimate is of a relatively substantial effect. If the male and female results were pooled a more stable estimate of reasonable magnitude would be seen. I think this finding should be discussed in the light of previous findings – the authors unfortunately refer only to not easily available reports of reviews of studies of passive smoking and COPD, but I think that with these data added to previous data there is a relatively strong case to be made that an effect on COPD is seen. This is of course not unexpected – COPD is considerably more responsive to tobacco smoke than coronary heart disease (see their table 10).

We believe that an RR with a 95% CI that includes 1.0 represents no relationship, whether the RR itself is above or below 1.0. All of the RRs for COPD have a 95% CI that includes 1.0. Note that Table 7 shows the 1973-98 RR(C/N) = 1.80 (0.78-4.17) for COPD and 0.23 (0.03-1.68) for lung cancer. We do not feel that we should state that 1.80 represents a positive relationship anymore than we should state that 0.23 represents a inverse relationship. The overinterpretation of statistically insignificant findings has been done far too much with previous ETS studies. However, since most of the RR(C/N)s and RR(E/N)s for COPD are larger than 1.0, we have modified that text to indicate that the COPD findings suggest a positive relationship and hope that this new wording is satisfactory.

Regarding previous findings on COPD, most of them involve asthma and lung function in children and pulmonary morbidity in adults, as described in references 2 and 7. We believe that this is the first cohort study to present RRs for COPD deaths related to spousal smoking and do not think too much should be made of RRs based on small numbers of deaths that are consistent with 1.0. Keep in mind, the primary focus of this paper is CHD.

Comments ...

Name: SJW Evans

Position: Prof of Pharmacoepidemiology

This paper has shown some considerable improvement, though the tables are rather extensive and, perhaps inevitably, indigestible.

The argument from the authors in favour of publication is resoanbly well put, though there are hints that the authors are less open-minded than they suggest.

The problems with misclassification of exposure are not dealt with as simply as they state. The lack of significant associations in shorter follow-up may be due to the low statistical power when any effect is unlikely to appear until follow-up is extensive.

We have modified our text slightly regarding the misclassification issue in order to be as balanced as possible. We feel that the consistent pattern shown in the short-term results of Table 9 is meaningful and interpreted correctly. The statistical power of our short term results is greater than that in most of the existing cohort studies.

The first phrase of the conclusions in the abstract might be deleted. It is likely to be misused; the results equally could be said not to rule out a causal relationship- they simply suggest that any

realtionship if it exists is not as high as some authors have suggested.

We think this phrase is appropriate and should be retained because it is supported by the results in the paper. But we have revised it to read: 'These results do not support a causal relationship between ETS and tobacco-related mortality, although they do not rule out a small effect.' If unsatisfactory, we are open to further modification by the Editors.

I believe that there are a number of studies that suggest that smoking of 40 or more cigarettes per day has a much greater increase in CHD than the RR of 1.9 in males and 2.4 in females found in this study. It remains possible that this study has under-estimated effects overall.

We do not believe there is an under-estimation of effects for active smoking. The 1960-98 CHD RRs in Table 10 are in good agreement with other CHD RRs reported for CPS I and other cohorts during the 1960s. The 1973-98 CHD RRs for CA CPS I defined as of 1972 (not shown) are larger than the 1960-98 RRs and are consistent with results from other cohorts begun in the 1970s. See "Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General, 1983," pps. 107, 118-119).

I am unceratin what the authors mean in the penultimate paragraph of the paper about "author bias". This should be referenced or amended.

The sentence has been clarified to state "author bias due to funding from the tobacco industry."

I would prefer to see that more reservations are included about the strength of conclusions that can be drawn from epidemiology of this type. The fact that others, based on equally weak studies, have drawn strong conclusions is not the point. We are concerned with this paper and it must make it clear that with observational data of this type, the conclusions must be temepered with acknowledgement of bias and confounding that limit strong statements.

We agree with the above comments and feel that the final two paragraphs of the Introduction and the final paragraph of the Discussion, as now written, include appropriate reservations. If unsatisfactory, we are open to further modification by the Editors.

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